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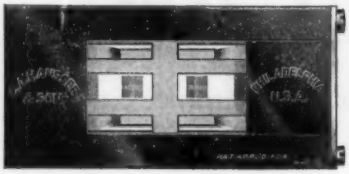

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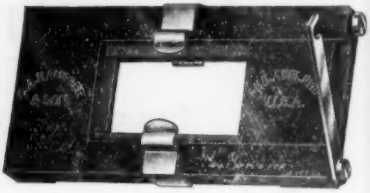

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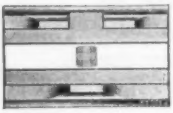

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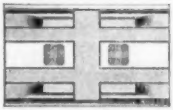

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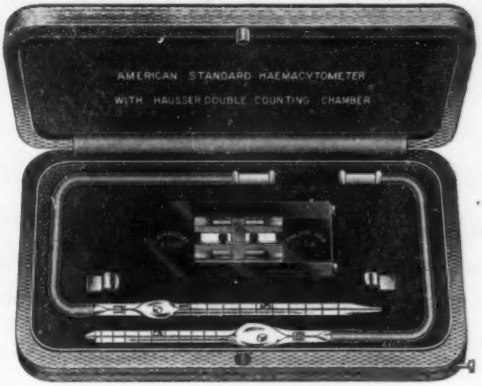

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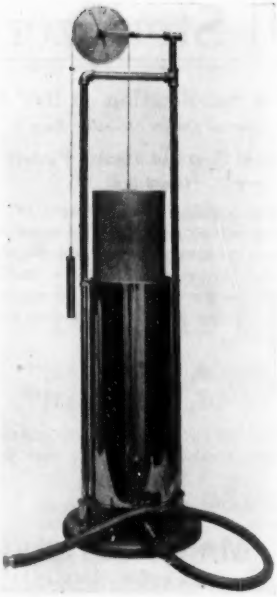

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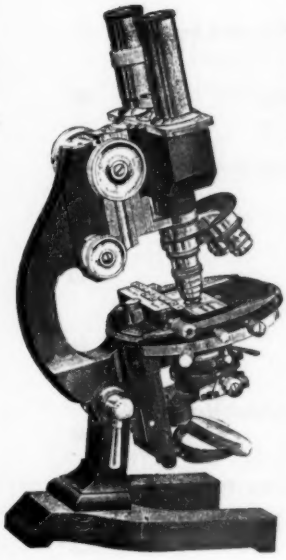

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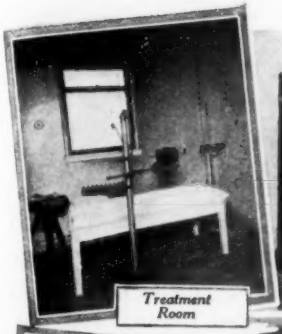

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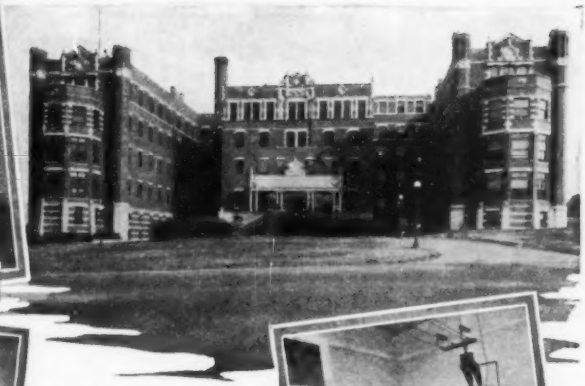

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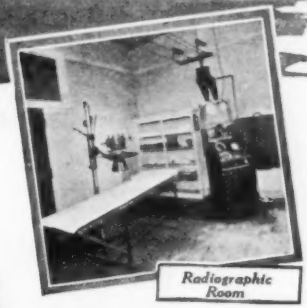

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AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JANUARY, 1922

ORIGINAL ARTICLES.

KIDNEY FUNCTION.[1]

By Alfred N. Richards, Ph.D.,

University of Pennsylvania, Philadelphia.

The subject of this paper, kidney function, is far too broad for discussion within the permissible limits of one lecture. I therefore propose to restrict what I have to say to the subject:

Glomerular Function and the Modes of its Regulation.—What I have to present is based upon work which has been proceeding with interruptions in the laboratory of pharmacology of the University of Pennsylvania for a number of years past; this work has been jointly carried on by Dr. O. H. Plant and myself during the years 1915 to 1920 and by Dr. Carl F. Schmidt and myself from September of last year until now. Their collaboration has been invaluable.[2]

I. Evidence that the Glomerulus of the Kidney is the Chief Structure Concerned in the Renal Elimination of Fluid from the Blood.—Until the classical work of the English anatomist William Bowman, published in 1842, there was no convincing evidence that connection existed between the Malpighian bodies and the uriniferous tubules. By extraordinary skill in dissection, Bowman proved that the capsule of the Malpighian body is the expanded extension of the membrane of the tubule. His first identification of the complete unit of structure by which urine is formed must therefore be regarded as the beginning of modern study of renal function.

[1] A lecture delivered before the Harvey Society, New York, February 26, 1921.

[2] The results of this work will shortly be published in the American Journal of Physiology.

Appended to Bowman's very complete description of the vascular arrangements of the kidney is a theory of the parts played by tubule and glomerulus in the formation of urine. He laid emphasis upon the structural similarity of the epithelium of the tubules and that of secreting glands, and drew the inference that the tubules eliminate from the blood "the peculiar principles found in the urine." He laid equal emphasis upon the dissimilarity of structure of tubules and capsule, and stated his conception of the significance of this dissimilarity in these words, which, though frequently quoted, may well be repeated:[3]

"Thus the Malpighian bodies are as unlike as the tubes passing from them are like the membrane, which, in other glands, screens its several characteristic products from the blood. To these bodies, therefore, some other and distinct function is with the highest probability to be attributed. The peculiar arrangement of the vessels in the Malpighian tufts is clearly designed to produce a retardation in the flow of blood through them. . . . It would indeed be difficult to conceive a disposition of parts more calculated to favor the escape of water from the blood than that of the Malpighian body. A large artery breaks up in a very direct manner into a number of very minute branches, each of which suddenly opens into an assemblage of vessels of far greater aggregate capacity than itself, and from which there is but one narrow exit. Hence must arise a very abrupt retardation in the velocity of the current of blood. The vessels in which this delay occurs are uncovered by any structure. They lie bare in a cell from which there is but one outlet, the orifice of the tube. This orifice is encircled by cilia in active motion directing a current toward the tube. These exquisite organs must not only serve to carry forward the fluid already in the cell, and in which the vascular tuft is bathed, but must tend to remove pressure from the free surface of the vessels, and so to encourage the escape of their more fluid contents. Why is so wonderful an apparatus placed at the extremity of each uriniferous tubule if not to furnish water to aid in the separation and solution of the urinous products from the epithelium of the tube?"

This is the first suggestion, founded, it is true, upon teleological argument from structure, that the glomerulus is the chief site of fluid elimination in the kidney. This suggestion developed into universal belief. The experiment which established its truth was not made until 1878, when Nussbaum[4] performed the operation in frogs of ligation of the renal arteries. This excluded the glomeruli from the circulation, but, owing to the double blood supply of the frog's kidney, did not abolish circulation in the vessels of the tubules. The result of this ligation was cessation of urine elimination.

[3] Phil. Tr. Roy. Soc., 1842, pp. 74 and 75.
[4] Arch. f. d. ges. Physiol., 1878, **16**, 139; 1878, **17**, 580.

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This observation, confirmed by others,[5] nearly approaches to direct proof of the assumption made by the older anatomists. Since it is completely in harmony with considerations of structure, since it is supported by a mass of less direct evidence obtained in other ways, and since there is no opposing evidence, so far as I am aware, we may regard this question, so fundamental to all further study of kidney function, as satisfactorily settled.

II. The Nature of the Process by which Fluid is Separated from the Blood in the Glomerulus.—In Bowman's statement of his hypothesis that the glomerulus separates water from the blood, no clear idea is given of the nature of the process. Unaware of the epithelium which covers the glomerular tuft, he regarded the capillaries as projecting naked into the capsule, and he speaks of the cilia at the orifice of the tubule as presumably having power of diminishing pressure on the capsular side of the capillary tuft and so facilitating escape of fluid from the blood. It seems to me that his words vaguely indicate the escape of fluid because of pressure within the capillary vessels.

There is no such vagueness, however, in Carl Ludwig's statement, made in 1844, of his conception of the process.[6] Using the anatomical facts demonstrated by Bowman and confirmed by himself, and applying principles of hydraulics, he stated that a significant pressure must be exerted by the blood within the glomerular capillaries upon their walls, and that this pressure must result in the filtration of a certain amount of fluid through them. He assumed that the membrane through which the fluid passed was normally impermeable to proteins, to fats and to salts which might be combined with these, and hence that the urine as formed in the glomerulus is a protein-free filtrate containing blood crystalloids in the proportion in which they exist free in the blood.

I have no wish to enter in great detail into a discussion of the evidence for and against the filtration theory; it has been adequately reviewed many times and forms part of current physiological teaching. Since in the development of what is to follow an appreciation of the chief elements of strength and of weakness in the filtration theory is necessary, I make no apology for briefly presenting the most important facts. The question whether the glomerulus filters fluid or secretes fluid is more than academic. A well-based conviction that the understandable process of filtration is the chief factor of glomerular activity permits clearly defined views concerning the nature of alterations in glomerular function which occur in health and disease. It carries with it as an inevitable corollary a conviction of reabsorption of both water and dissolved substances

[5] Adami: Jour. Physiol., 1885, **6**, 582. Beddard: Ibid., 1902, **28**, 20. Cullis:, Ibid., 1906, **34**, 250. Bainbridge, Collins and Menzies: Proc. Roy. Soc. B., 1913, **86**, 355.

[6] Wagner's Handwörterbuch der Physiologie, 1844, **2**, 637.

from the lumen of the tubule, for no other process could account for the difference in composition between a blood filtrate and the urine as it leaves the kidney. Absence of such conviction, on the other hand, necessitates refuge in the conception of "secretion," a word implying ignorance or uncertainty of processes involved and an ill-defined point of attack on the further questions of alterations in renal function.

There are three groups of experiments which, I think, form the chief support of the filtration theory.

First, experiments which demonstrate the parallelism between urine elimination and renal blood-pressure. These include the experiments in Ludwig's laboratory by Goll,[7] showing that changes in general arterial blood-pressure, induced by vagus stimulation, hemorrhage, injection of blood or ligation of large arterial trunks caused changes in a similar sense in urine flow; and those by Hermann,[8] in which diminution in urine was found to follow partial obstruction of the renal artery. They include also numerous experiments which developed from Claude Bernard's discovery of vasomotor nerves, experiments in which the nerve supply of the kidney was either divided or stimulated, and resulting increase or decrease in urine found to be attributable to dilatation or constriction of the vessels in the kidney.[9] It was recognized by Ludwig and his colleagues that such changes in the renal circulation as were studied in these experiments involved alterations not only in renal blood-pressure but in velocity and volume of renal blood flow as well. Reasons were adduced (Hermann) for belief that the effective variable in these experiments was that of pressure. The force of the experiments and the influence of Ludwig were such that his conception of glomerular filtration and tubular reabsorption became the generally accepted view.[10]

The second group of experiments to which I refer is based upon this principle of physics: that in order to separate a dissolved substance from its solvent by filtration through a membrane, permeable by the solvent but not by the dissolved substance, filtration pressure must be greater than the osmotic pressure of the dissolved substance. Tammann,[11] of Rostock, in 1896 showed that the osmotic pressure of all the substances dissolved in the blood plasma was nearly eight atmospheres (5840 mm. Hg,); that the osmotic pressure of the organic solids of blood plasma amounted to 840 mm. Hg. (He regarded the osmotic pressure of proteins as negligible.)

[7] Ztschr. f. rat. Med., 1854, **4,** 78.

[8] Sitzungsber. d. kais., Akad. d. Wiss., Wien, 1862, **45, 2,** 317.

[9] Bernard: Leçons sur les proprietes physiologiques des liquides de l'organisme, 1859, **2,** 169. Eckhard: Beitr. z. Anat. u. Physiol., 1869, **4,** 155. Ustimowitsch: Ber. u. d. Verh. d. k. Sachs. Gesell. d. Wiss. z. Leipsig (Math.-phys. Cl.), 1870, **22,** 430. Grützner: Arch. f. d. ges. Physiol., 1875, **11,** 370.

[10] Cf. Heidenhain: Hermann's Handbuch der Physiologie, **5, 1,** p. 318.

[11] Tammann: Ztschr. f. physikal. Chem., 1896, **20,** 180.

Since no pressures of this order of magnitude are to be found in the animal circulation, he concluded that the only substances of plasma which could physically be held back in the glomerulus are the proteins; hence the fluid separated in the glomerulus must be the water of the blood containing all dissolved substances except proteins.

Starling,[12] in the same year, discovered that the osmotic pressure of plasma proteins amounted to from 30 to 40 mm. Hg. He showed that a force of this magnitude exerted by substances retained within the bloodvessels was sufficient to explain in part the absorption of fluid from tissue spaces into the bloodvessels. In 1899 he extended this reasoning to the explanation of glomerular function.[13] By improved method he redetermined the osmotic pressure of plasma protein and obtained the figure 25 to 30 mm. Hg. If the osmotic pressure of plasma protein is the force which blood-pressure must overcome in order to filter fluid from the blood in the glomerulus, then it should be found that the lowest arterial blood-pressure compatible with urine elimination should be slightly above this. His own experiments and those of many others showed that urine ceased to be eliminated when arterial pressure fell below 40 mm. Hg. Further, if glomerular function is filtration then the difference between arterial blood-pressure and the maximum pressure in the ureter against which urine can be eliminated should be almost that of the osmotic pressure of the proteins. He found this difference during profuse diuresis in the dog to be 32 to 43 mm. Hg. These results, confirmed and extended by Knowlton,[14] are so completely in accord with the demands of the filtration theory that they furnish the strongest support for it.

The third group of experiments in this connection are those of Barcroft and Straub[15] made in 1910. They applied to the kidney the methods so fruitfully developed by Barcroft for estimating the rate of metabolism of organs. Saline diuresis—*i. e.*, diuresis following injection of sodium chloride solutions—was found to be unaccompanied by increase in utilization of oxygen or formation of carbon dioxide. Knowlton and Silverman[16] later showed that this was true for diuresis following injection of pituitrin. The conclusion was drawn that physical factors rather than "vital" or "secretory" are concerned in this increase in kidney function, the inference being that filtration is increased.

These are the facts which to my mind most nearly constitute "proof" of the filtration idea: they are reinforced by considerations of the structure of the glomerulus and by observations in other directions; that the more rapidly urine is eliminated the more nearly it comes to resemble a filtrate from the blood; that the

[12] Jour. Physiol., 1896, **19**, 312.
[13] Ibid., 1899, **24**, 317.
[14] Ibid., 1911–12, **43**, 219.
[15] Ibid., 1910–11, **41**, 145.
[16] Am. Jour. Physiol., 1918, **47**, 1.

glomerular fluid is alkaline, as tested by intravital indicators; that the osmotic pressure and chloride content of the cortex more closely resemble that of the blood than does that of the medulla. This collection of facts led Bayliss to write, in 1915, "The evidence for this (glomerular filtration) is overwhelming;"[17] and Cushny, in his development of the "modern" theory of urine formation, to accept glomerular filtration as a fundamental truth.[18]

It is easy to develop conviction of the truth of filtration by study of the work to which I have alluded. It is not so easy to hold it after consideration of some of the questions which have been put to the filtration theory and have not found satisfactory answer.

Heidenhain, in 1874, began the publication of his work on the kidney, from which developed the so-called Bowman-Heidenhain theory. As is well known he injected indigo carmin into the circulation and failed to find traces of it in the capsule or any staining of glomerular structures by it. Since it was to be found in the lumen of the tubule, and since the tubular epithelium was stained by it, he was forced to conclude that it had been secreted by the tubules and had not been filtered by the glomerulus.[19] This observation led him to further results which obliged him to deny the filtration-reabsorption theory completely and to attribute urine formation to secretory processes in the epithelium of glomerulus as well as of tubule—*i. e.*, to processes not explainable by known physical or chemical laws.

Most of Heidenhain's contentions have since been successfully met by adherents of the filtration idea. Cushny's monograph contains an admirable exposition of this subject. One objection, however, seems to me to have been least satisfactorily answered, and it happens that this is the one to which Heidenhain himself attached the most weight. It concerns the effects of compression of the renal vein upon urine elimination. The following is a translation of his own words.[20]

"But if mechanical filtration does really occur, then elimination of water must always increase with the pressure. An old experiment shows that this is not so. For if the pressure in the glomeruli is increased by partial or complete occlusion of the renal vein an immediate diminution in urine occurs.

"This fact contradicts the pressure hypothesis in the most abrupt (schroffstem) manner. . . .

"If it is considered that increase in aortic pressure, if only a few millimeters, often causes a considerable increase in urine, and that after partial or complete occlusion of the renal vein a considerable rise of pressure within the glomerular vessels must occur, then it is

[17] Bayliss: Principles of General Physiology, 1915, p. 355.
[18] Cushny: The Secretion of Urine, 1917.
[19] Heidenhain: Arch. f. mik. Anat., 1874, **10**, 1.
[20] Heidenhain: Hermann's Handbuch der Physiologie, 1883, **5**, pt. 1, pp. 324, 325.

apparent that here is a phenomenon completely inexplainable by the filtration hypothesis."

Ludwig[21] was aware of this objection and had met it by demonstrating that complete obstruction of the renal vein in the living animal caused such swelling of the veins within the kidney that the tubules were compressed and their lumina obliterated. Obviously, no urine could issue from the kidney under these circumstances. It appears that Heidenhain[22] accepted Ludwig's demonstration of the effects of complete occlusion, but he did not regard it explanatory of the events which follow partial closure of the vein. Slight obstruction of a degree sufficient to lessen but not to suppress urine flow could not cause such lessening by engorgement of veins with resulting closure of tubules. The fact that urine continued to flow, though at a lower rate, indicated that the tubules were patent. Paneth's[23] later experiments, showing the possibility of diuresis by sodium nitrate during constriction of the renal vein, confirmed this conclusion. For this reason Heidenhain regarded the failure of slight compression of the renal vein to increase urine flow as the strongest argument against the filtration hypothesis, and it was this that led him to the belief that the velocity of blood flow through the glomerulus, rather than the pressure of blood within it, was the determining factor in the first formation of urine in the kidney.

In answer to this objection it was pointed out by Tammann[24] that if fluid is filtered from the blood in the glomerulus any stagnation of flow in the glomerulus, as by venous obstruction, would lead to rapid increase in osmotic resistance to filtration. It has not been shown that this factor can be so effective during partial occlusion of the vein as to more than compensate for the increased glomerular pressure. It has been suggested by De Souza[25] that blocking of the renal vein causes reflex constriction of the renal artery, but no evidence of this has been presented so far as I am aware. Consideration of these matters leads me to think that the argument against filtration, based upon the effects of obstruction of the renal vein, has not been adequately answered.

Another series of obstacles in the way of unreserved acceptance of the filtration hypothesis has arisen from the comparison of urine elimination with vascular conditions in the kidney, as shown by oncometer records of kidney volume, and these difficulties have increased with the later development of improved methods of estimation of the flow of blood through the kidney.

The oncometer, first applied to the study of renal physiology by Roy and Cohnheim in 1883, registers changes in the total volume of the kidney; these changes are commonly referred to alterations in

[21] Sitzungsber. d. k. Akad. d. Wiss. zu Wien, November, 1883.
[22] Hermann's Handbuch, **5, 1,** p. 317. Cf. also Paneth, pp. 550, 551.
[23] Arch. f. d. ges. Physiol., 1886, **39,** 515.
[24] Loc. cit.
[25] Jour. Physiol., 1900–01, **26,** 139.

the state of the renal bloodvessels. In 1900 and 1901 Gottlieb and Magnus[26] made an admirable series of observations on blood-pressure, kidney volume and urine flow during diuresis. Following the injection of single doses of diuretics, remarkable parallelism between urine elimination and vascular dilatation, as shown by the oncometer, was observed; but when repeated dosage was given this parallelism failed. Diuresis was observed to increase in some instances at a time when renal vessels, as shown by the oncometer, were constricting; in others it diminished while renal vessels were similarly shown to be dilating.

These objections were materially supported by the late Professor Brodie, of Toronto. He extended the observations of Magnus and Gottlieb by including in his experiments direct estimations of blood flow through the kidney. In his lecture before the Harvey Society in 1910[27] and in his Croonian lecture of 1911[28] he stated that, following the injection of diuretics, in five experiments he had observed the following coincident phenomena: Increased kidney volume (indicative of dilatation of vessels); diminished blood flow (indicative of constriction of vessels); increased urine elimination.

Both Magnus and Brodie apparently accepted the common implication of vascular changes, namely, that dilatation of renal vessels means rise of intraglomerular pressure, and constriction of renal vessels means decrease in intraglomerular pressure; and hence their observations became so self-contradictory when viewed in the light of the filtration hypothesis that they were forced to abandon it.

In the considerations thus far advanced I have hoped to show that in spite of the array of strength back of the belief that urine is first formed in the glomerulus by a process of filtration, sound observations exist, made by most competent observers, which have forced them to deny it. Concern over these difficulties, and the necessity of a conviction concerning them, led to a series of experiments by my colleagues and myself which have, we think, a direct bearing on their solution.

In Hermann's[29] second paper on kidney function, published in 1862, it is stated that "The effect of pressure changes as compared with other factors which modify urine excretion can only be brought out clearly when one has control over the blood entering the vascular system and can regulate it at will." I cite this to show that the desire for some sort of artificial experimental control over circulatory conditions in the kidney in order to reduce the number of variables in an experiment is very old. Hermann devised a clamp by which the caliber of the renal artery could be narrowed, hoping to identify the effects of lowered renal blood-pressure by this means; somewhat

[26] Arch. f. exp. Path. u. Pharm., 1901, **45,** 223.
[27] Harvey Lectures, 1909–10, 5th series, p. 81.
[28] Brodie: Proc. Roy. Soc., B., 1913–14, **87,** 571.
[29] Loc. cit.

similar experiments have more recently been made. A defect in such experiments, recognized by their authors and emphasized by Heidenhain, is that such a device simultaneously alters both blood-pressure and blood flow in the renal circulation, and there is no direct means of distinguishing effects due to one of these to the exclusion of the other.

During the years 1912–14, C. K. Drinker and I designed and constructed an apparatus for the perfusion of isolated surviving organs capable of pumping a pulsating stream of fluid in a manner similar, as pulse records showed, to that of the heart.[30] Its volume output was controllable within fairly wide limits. With it we perfused the dog's kidney and were able to show that the fluid which issued from the ureter was urine and not a transudate. In 1914–15 Dr. O. H. Plant and I elaborated a method for perfusing the rabbit's kidney *in situ* with this apparatus.[31] Our method possessed these advantages and possibilities:

1. The perfusion fluid was the undiluted blood of the animal whose kidney was perfused plus blood taken fresh from another animal of the same species. Hirudin was used to prevent clotting.

2. The artificial circulation through the perfused kidney was inaugurated without any interruption in blood flow through the organ, and in some instances urine flow continued without interruption during the change from normal to the artificial circulation.

3. While the output of the perfusion apparatus could be varied at will, for any particular adjustment the output was constant, regardless of the resistance offered by the vessels through which it drove the blood. It was thus possible to alter pressure by various means within the kidney vessels without simultaneous alterations in volume flow or velocity of blood in them. It is in this respect that our experiments differed essentially from those of earlier workers.[32]

The means which we used to alter pressure in the circulation of the perfused kidney were these: stimulation of the splanchnic nerve; injection of adrenalin; partial occlusion of the renal vein.

Since all of these agencies raised pressure in the renal circulation, and since the conditions of our experiment were such that they could not materially change the blood flow, we seem justified in attributing such results as were obtained to changes in renal blood-pressure.

Each of the three agencies tested increased urine formation in a number of experiments practically without exception.

It will be noted that among these agencies employed is venous obstruction, which in the intact animal always causes diminution of urine, a fact regarded by Heidenhain as the strongest argument

[30] Richards and Drinker: Jour. Pharm. and Exper. Ther., 1915, **7**, 467.
[31] Richards and Plant: Ibid., p. 485.
[32] Richards and Plant: Am. Jour. Physiol., 1917, **42**, 592.

against filtration. In our experiments, in which it increased urine, there was no stagnation of blood in the glomerular capillaries which might neutralize the effects of increased glomerular pressure as a filtering force. The experiment seems to me to remove the force of Heidenhain's objection and to confirm the suggestion that in the intact animal partial occlusion of the renal vein so lessens the rapidity of renewal of blood in contact with the glomerular endothelium that the effect of increased filtering forces is nullified.

III. Regulation of Glomerular Pressure.—The experiments just described have served us in three ways: they yield evidence that rise of pressure alone in the renal circulation can cause increase in urine; they point to a solution of Heidenhain's difficulty which is consistent with the filtration theory; and they provide a point of departure for an analysis of the effects of increased renal pressure. In this last connection the action of adrenalin has been most useful.

If the vascular reaction of a perfused kidney to minute doses of adrenalin is compared with the same reaction of another structure similarly perfused—*e. g.*, the leg—a striking difference appears. Any dosage of adrenalin which causes constriction of the vessels of the leg also causes diminution in volume of the leg, as shown by the oncometer. When a perfused kidney is similarly tested it is found that large dosage of adrenalin causes a similar effect, *i. e.*, constriction of vessels as shown by rise of perfusion pressure and shrinkage of volume of the kidney; but smaller doses, which still cause some degree of constriction of vessels, as shown by the perfusion pressure, cause either no change in or distinct swelling of kidney volume.

In this experiment with the kidney we have an apparent paradox of coincident constriction of vessels, as shown by rise of perfusion pressure, and dilatation of vessels, as shown by swelling of the kidney.

The only reasonable explanation of this paradox which has occurred to us is this: between the afferent and efferent vessels of the glomerulus is interpolated the distensible capillary area of the glomerular tuft. The walls of the afferent and efferent vessels both contain smooth muscle; both are supplied with nerve fibrils (presumably sympathetic), ending in contact with the muscle cells.[33] If under the conditions of our experiment the efferent vessel were constricted a passive rise of pressure must occur in the glomerular capillaries proximal to it, and the distention of these, thus brought about, might cause swelling of the kidney. In support of this view we recall the generalization which Elliott's work has established, namely, that the action of adrenalin is equivalent to stimulation of sympathetic innervation: and we have an observation of our own, made with the frog's kidney, which shows unmistakably that adrenalin has the power of constricting bloodvessels peripheral to the glomerulus.

[33] Smirnow: Anat. Anzeiger, 1901, **19**, 347.

In the minds of many physiologists a certain stigma appears to attach to perfusion experiments with isolated organs when the attempt is made to apply results so obtained to the interpretation of events within the intact animal body. If it were possible to demonstrate constriction of the efferent vessel by adrenalin in the intact animal with associated diuresis the force and usefulness of the experiments just cited would be increased. Reason for thinking that this might be possible seemed to exist. The efferent vessel of the glomerulus is a narrower tube than the afferent vessel. A constrictor influence, acting alike on both, would therefore produce a greater increase in frictional resistance to blood flow in the smaller (efferent) vessel; for this reason it seemed probable that very minute amounts of constrictor substances might, by more effective constriction of the efferent vessel, produce simultaneously three effects in the intact animal: diminution in blood flow through the kidney by constriction of efferent vessel; increase in urine by increased glomerular pressure; swelling of the kidney by distention of the glomerular capillaries. The event showed that this combination could be demonstrated following minute, but clearly constrictor, doses of adrenalin and pituitrin.

These experiments seem to me to yield evidence not only that the glomerular process is filtration but also that intraglomerular pressure—filtration pressure—is regulated by the relative degree of constriction or dilatation of the afferent and efferent vessels. This latter belief is intimated in a statement by Ludwig[34] in 1856:

"Since the afferent and efferent vessels of the glomerulus, as well as the roots of the renal vein, contain muscle within their walls, the possibility exists that the blood stream in the kidney changes according to the contractions of these muscles, even though the movements of the heart and the general circulation in the organism remain unchanged."

In connection with the action of constrictor substances, like adrenalin and pituitrin, it becomes apparent how it is possible for the same substances in different dosage to produce opposite effects. Minute amounts causing more effective constriction of the smaller efferent vessel may increase urine by increasing intraglomerular pressure; larger amounts, by constricting both afferent and efferent vessels, may diminish urine by decreasing ingress to the glomerulus and so lessening both intraglomerular pressure and velocity of flow. The literature shows that small dosage of adrenalin may cause diuresis. Nothing is easier to determine than that larger doses cause partial or complete suppression of urine. Similar apparently contradictory evidence concerning pituitrin can be found.

Permit me now to revert to Brodie's statement of a group of occurrences which he regarded as completely inconsistent with the

[34] Lehrbuch der Physiologie des Menschen, 1856, **11**, 257.

filtration theory: diminished blood flow through the kidney, increase of kidney volume and increase in urine. This group of occurrences, as we think our experiments indicate, is precisely that which would be expected as a result of preferential slight constriction of the efferent vessel, and instead of being inconsistent with the filtration theory is demanded by it.

From this reasoning it would seem as though any substance which is constrictor to renal vessels should, in suitable high dilution, show evidence of diuretic power unless it lowers general blood-pressure or diminishes permeability of the glomerular membranes. This supposition is now being tested.

I am inclined also to suggest another generalization, based upon this evidence that intraglomerular pressure may be altered by more effective action of a substance upon the efferent than upon the afferent vessel. It concerns the action of arterial dilator substances in general. If it be agreed that glomerular urine is a protein-free filtrate from blood, then it follows that any substance in solution in the blood which causes dilatation of renal arterioles, and which in part passes out of the blood with the glomerular filtrate, must from these facts be potentially diuretic; for its effective concentration will be greater in the blood in the afferent vessel than in the blood in the efferent vessel; and its dilator action will be greater on the afferent than on the efferent vessel, and for this reason alone intraglomerular pressure must rise.

It should be noted that by effective concentration I mean concentration in relation to the colloids of the blood.

Without having the direct evidence to support this idea, I venture to present it in the belief that it is applicable to the glomerular behavior of a large number of substances—water, urea, the caffein series, salts, etc., all of which are vasodilator, and all of which, we believe, leave the blood stream as it passes through the glomerulus.

If we regard the renal arterioles as very sensitive both to constrictor and dilator substances, as they most certainly are, and if we admit the possibility of such preferential action as I have indicated on either efferent or afferent vessel, we must see in this a very delicate mechanism whereby intraglomerular pressure, and hence the first formation of urine is regulated in accordance with the chemical composition of the blood.

IV. Description of Glomerular Circulation.—In this description of experiments, both of our own and of others which concern the nature of glomerular function and its mode of regulation, an implication has been permitted which now appears to me to require correction. Its correction does not, I think, materially alter the force of the conclusions which have just been drawn, but it adds an element in the conception of glomerular regulation which may be of greater importance.

The kidney contains a great number of urine-forming units. The

number of glomeruli in the cat's kidney has been estimated at 16,000; in the kidney of a dog weighing 11 kilos, 150,000; in the human kidney, 2,000,000.[35] For each glomerulus there is a tubule. It seems to me that it has been tacitly assumed in the great bulk of writing on kidney function that the circulation through all of these units is at least roughly uniform—that they take equal part in the sum of activities which made up the total function of the whole organ. I have found one explicit statement of another conception: In Hermann's first work (1859) on kidney function he noted that the two kidneys may eliminate different amounts of urine, and he stated that it was simplest to assume that all parts of the kidney do not act to the same degree all of the time—that one part of the excreting surface may rest or be active while another part is in reserve.[36]

We have observations which indicate that this is a true conception.

In the development of the idea that glomerular pressure may be regulated by the degree of constriction of its efferent as compared with its afferent vessel, it became highly desirable that we get evidence as direct as possible concerning changes in size of the glomerulus during the action of adrenalin under controlled conditions of blood flow. In 1919 Krogh, of Copenhagen, published his extremely important paper on the behavior of capillaries in muscle.[37] He used methods of direct microscopical observation of muscles illuminated either by transmitted or reflected light. It occurred to us that the use of the same method might enable us to see the glomeruli of the kidney in operation, provided we could find a kidney sufficiently translucent to permit a certain penetration of light rays. In September of 1920 Dr. Schmidt and I found that the frog's kidney fulfills this demand. When we focused the light of an arc lamp or a 1000 watt "Mazda" lamp upon the ventral surface of an exposed frog's kidney *in situ*, the low power of the microscope showed in the interstices of the radicals of the renal veins nests of capillaries which to our view and that of competent microscopists could be nothing else than glomerular tufts. It soon became possible to distinguish the outline of the capsule, in many cases the entrance of the afferent vessel, and in not a few instances the exit of the efferent vessel as well. Because not all of these structures had the same appearance and to prevent an egregious error, we spent some time in attempts to identify a certain group of glomeruli in the living kidney, to follow this group through processes of fixation and embedding in order to prepare a stained section which should contain the structures examined in the living kidney. With the aid of Dr. B. Lucke this was successfully done. This identifica-

[35] Cited from Cushny: The Secretion of Urine, p. 5.

[36] Sitzungsberichte d. k. Akad. d. Wiss. zu Wien, Math.-Naturwiss. Cl., 1859, **36**, 349.

[37] Jour. Physiol., 1919, **52**, 409.

tion has given a sense of security concerning previous and subsequent observations which we might not otherwise have had.

When the lateral border of the ventral surface of the frog's kidney is observed in this way, the large renal veins and their tributaries are most prominent. Arterial branchings and the divisions of the renal portal vein, being deeper in the kidney, are less obvious. Details of the tubules are commonly indistinct. In the interstices of the veins are seen the glomerular tufts. They vary in size from 80 to 250 microns in diameter. Some show a great multiplicity of tortuous narrow channels, each of a diameter sufficient to permit passage of one red cell. The capillary wall is not easily seen. The blood flow through these channels is oftentimes bewilderingly rapid. In other instances the appearance is of another type: instead of a multiplicity of channels only one or two capillary loops are visible; these have wider diameter and show sluggish flow of more densely packed corpuscles. In the more slowly flowing blood streams pulsations are apparent; in the more rapidly flowing stream it may not be. Between these two extremes intermediate variations occur.

Concerning the problem which was the impetus for beginning these observations—*i. e.*, the question whether the glomeruli could be seen to swell as a result of the constrictor action of minute amounts of adrenalin upon the efferent vessel—the answer is still indeterminate. A series of measurements by Dr. Schmidt of glomerular diameters before, during and after the injection of doses of adrenalin of the order of 0.1 cc of 1 to 1,000,000 showed swelling, and in so far were confirmatory of our conclusions drawn from the mammalian experiments. But since a distinct improvement in the general circulation resulted from this injection the increased glomerular size may have been due to this. Before a final answer can be obtained the experiment must be performed on the kidney, perfused with blood at a constant rate. This experiment has not yet been made. Other features of the glomerular circulation seemed to demand more immediate study.

In our earliest experiments the variability of our preparations was striking. In some preparations as many as eight glomeruli could be counted in a field of 2 mm. diameter; in others only three or four in the whole kidney, in so far as it was accessible to inspection. Our frogs were pithed, and if two or three drops of blood were lost in this operation the number of glomeruli to be found in the kidney was small. If, however, such a frog were immersed in a saline bath, or if his abdominal cavity were filled with isotonic salt solution, the number of visibly active glomeruli increased.

Acting on the suggestion which this fact afforded, we have made a series of counts of the glomeruli which show active circulation under varied conditions.

Bits of silk thread were laid transversely across the surface of the kidney at approximately equal distances of about 2 mm.

(the diameter of our low-power field). From five to eight fields were thus separated for ease in counting. A bit of cover-slip was lightly laid over these, both to prevent displacement of threads and to avoid surface glare.

I shall cite figures to show alterations in the number of glomeruli in which blood was flowing before, during and after the introduction of various substances to be mentioned.

1. *Isotonic Salt Solution.*—As has been mentioned, salt solution is absorbed from the open abdominal cavity of the frog, and as a result circulation improves if it has been lessened from hemorrhage. These figures illustrate: Soon after preparation five fields showed 5 active, 8 inactive, total 13 glomeruli. Thirty minutes after salt solution had been introduced into the belly the same fields showed 28 active, 0 inactive, total 28 glomeruli. (By "active" glomeruli we mean those showing active circulation.)

2. *Injection of Blood.*—0.5 cc of whole blood was taken from the aorta of one frog and immediately injected into the anterior abdominal vein of a frog, whose glomeruli had been counted. Before injection, active glomeruli 10, inactive 27, total 37; five minutes after injection, active glomeruli 39, inactive 9, total 48.

3. *Injection of Isotonic Salt Solution.*—0.5 cc of 0.6 per cent. Before, 41 active, 9 inactive, total 50; ten minutes later, 54 active, 8 inactive, total 62; twenty minutes later, 44 active, 6 inactive, total 50.

4. Then *urea* 0.1 cc 20 per cent. After, 65 active, 2 inactive, total 67.

5. *Caffein,* 7 fields counted: Before injection, 81 active, 11 inactive, total 92; 0.1 cc 2 per cent *caffein,* five minutes later, 104 active, 0 inactive, total 104.

6. *Glucose.*—0.1 cc, 10 per cent glucose: Before injection, 31 active, 12 inactive, total 43. Followed by progressive increase in number of active until thirty-five minutes after, 62 active, 3 inactive, total 65.

7. *Hypertonic Sodium Sulphate* (5 per cent): 0.1 cc. Before, 6 active, 0 inactive, total 6; after thirteen minutes, 51 active, 0 inactive, total 51.

8. *Adrenalin* constrictor dose 0.1 cc, 1 to 100,000: 3 fields; before injection, 49 active; immediately after, 12 active; seven minutes later, 48 active.

9. *Pituitrin:* Constrictor dose, 0.1 cc 1 to 10 dilution of pituitrin "S." Before, 14 active, 5 inactive, total 19; after, 0 active, 16 inactive, total 16; later, 5 active, 12 inactive, total 17.

These and many similar observations have led to the conclusion that even under the most favorable of operative conditions, *i. e.,* with the least loss of blood, all the glomeruli of the kidney of the frog do not receive blood simultaneously. Conditions which depress the circulation, such as blood loss or destruction of the cord, or

agencies which constrict bloodvessels in the kidney, such as constrictor doses of adrenalin or pituitrin, lessen the number of glomeruli which receive blood. Plethora, absorption or injection of isotonic salt solution, hypertonic NaCl, hypertonic sodium sulphate, urea, glucose and caffein—all are capable of impressively increasing the number of glomeruli which receive blood at one time.

Not only is the number of glomeruli showing active circulation altered by the agencies which I have mentioned, but also the number of capillary loops within a single glomerulus which take part in the capillary blood flow. Earlier in this section I referred to glomeruli of two rather widely different aspects in so far as blood flow through them is concerned; one in which narrow rapidly flowing currents of blood indicate a complex network of tortuous channels; others in which one or two loops only are visibly filled with blood and in these blood usually flows more slowly and in a wider stream. The dilator agencies, urea, caffein, etc., mentioned above have the power of transforming a glomerulus of the latter type into one of the former.

Adrenalin, on the other hand, in constrictor dosage transforms a glomerulus showing a multiplicity of channels with rapid flow into one with fewer patent capillary loops and slow flow.

This indicates that just as all glomeruli in a kidney do not receive blood at once, so too in a single glomerulus not all the capillary loops need be patent at one time. Dilator (diuretic) agencies increase the number of capillaries in the glomerulus through which blood is flowing; constrictor substances and depression of the general circulation lessen the number.

Another characteristic of glomerular blood flow in the frog's kidney is that it is not always continuous but may be intermittent. Intermittence of glomerular flow is more liable to occur in a kidney showing active rapid circulation than in one in which blood flow is more sluggish. It was first observed by us in frogs after improvement of the circulation following absorption of salt solution; it has, however, been observed in frogs subjected to no other preparation than that required for looking at the kidney. The intermittence of blood flow may be of different types; in some instances there may be diminution in all and cessation in many at the same time, as though resulting from an influence outside of the kidney, as, for example, by changes in the general circulation or as a result of nervous stimuli to the bloodvessels. This type is easily understandable.

What we think of, however, as true intermittence is less easy to comprehend: two adjacent glomeruli may be situated within a few microns of each other; blood flow in one may stop completely, to be resumed after an interval, without interruption or even perceptible alteration in flow in the other. This phenomenon may be multiplied so that in a favorable field one sees a lively series of irregular interruptions in flow through the various glomeruli visible.

The interruptions bear no relation to the heart-beat. The intermittence of one glomerulus was timed with a stop-watch—15 seconds on; 12 seconds off; 27 seconds on; 11 seconds off.

In another, 103 seconds on; 10 seconds off; 90 seconds on; 45 seconds off.

In another preparation, 5 glomeruli were watched at once: Nos. 3, 4 and 5 stopped at the same time; Nos. 1 and 2 kept on actively. After three minutes No. 4 begins; Nos. 3 and 5 are blank.

We have tried to get a graphic representation of this phenomenon. A keyboard with five keys was connected each with a signal magnet arranged to write on a drum. Five glomeruli in a field were chosen and a key assigned to each. Discontinuance of flow was registered by pressing the key and keeping down until the flow resumed. The recorder also noted on the drum obvious variations in rapidity of flow which could not be designated as complete cessation or resumption. Charts were then made of these records.

Study of these charts forced the conclusion that while at times there are interruptions common to all, in the main the circulatory activity of one is independent of others; and the inference is drawn that a local regulatory mechanism must exist analogous to that shown by Krogh to exist in muscles.

Preliminary attempts to gain deeper insight into the circumstances of this phenomenon have been made. Not very much can safely be stated at present. We are sure that the phenomenon of intermittence persists after complete destruction of the whole central nervous system—brain and cord. There is evidence that intermittence of the glomerular circulation is commonly associated with simultaneous and synchronous intermittence of the afferent vessel. In this connection it is very striking that when flow stops abruptly in a single active glomerulus, corpuscles do not remain stagnant in its capillaries; they may remain for an instant, then they fade out of view and the whole glomerulus may become invisible. This must mean that the capillaries of the glomerulus possess power of independent contraction capable of emptying their lumina after blood has ceased to flow. This statement must be held as applicable to the afferent and efferent vessels, since they as well as the glomeruli are emptied when blood flow stops. Dr. Schmidt has made one observation which we hope to repeat: In one instance capillary flow in the glomerulus ceased abruptly and blood cells disappeared from it; but the afferent vessel remained full of blood, the corpuscles oscillating back and forth at the entrance of the glomerulus until presently the glomerular capillaries opened and flow through the whole structure resumed.

This emptying of the capillaries after cessation of flow—indicating, as we believe, independence of contractility of their walls—is much less marked or may be absent in the dilated sluggishly flowing capillaries of some of the glomeruli to which reference has been

made. These are likely to remain engorged with cells when the flow ceases. We take this to mean that there are normal differences in tonus and normal variations in tonus.

We do not yet know what the nature of the influence which regulate this tonus is.

Making the assumption that these observations are applicable to the mammalian kidney, they give us a conception of glomerular circulation different from that which I had previously held. Instead of a uniform circulation of blood through all the glomeruli, varying with general and renal blood-pressure, we conceive of a circulation, restricted under conditions of moderate blood flow to only a fraction of the glomeruli; and instead of equal circulation through all of the capillaries of a single glomerulus, we conceive of the possibility of restriction of flow through a fraction of the available pathway. This restriction in number of functioning glomeruli and in patent capillary loops may be brought about by general influences (circulatory and nervous) brought to bear from outside the kidney and unequally effective in different units of the kidney through anatomical differences, such as length of vessel; in addition we think of the restriction as due to a local, peripheral control of contractile power, not only of afferent and efferent vessels, but of the intervening capillaries as well. The phenomenon of intermittence permits us to think of alternating rest and activity of glomerular structures and prevention of damage such as would conceivably result from prolonged interruption of blood flow.

The phrases "dilatation of the kidney vessels" and "constriction of the kidney vessels" come to mean not only the increase and decrease in volume and rate of a stream already flowing, but also the increase and decrease in actual number of functioning glomeruli and of open glomerular capillaries. The possibilities in the direction of increase or restriction of filtering surface become more impressive.

On this basis it is not difficult to understand how relatively enormous changes can take place in glomerular blood flow without correspondingly great changes in the size of the kidney as registered by the oncometer, for obviously the capsule does not collapse when flow through the tuft ceases. It is easy to understand and to accept such puzzling experiments as those of Loewi—in which the ability of blood flow to increase under the influence of caffein in a kidney embedded in plaster of Paris was demonstrated.

It becomes easier to understand how a kidney might eliminate from blood of the same composition and in equal spaces of time urine of widely different composition, for a urine issuing as the result of highly active blood flow and high glomerular pressure in a smaller number of glomeruli must be different from that which issues as the result of slower blood flow and lower glomerular pressure from a larger number of glomeruli. The resorptive powers of the tubules would be effective to different degrees.

The difficulty of injecting the glomeruli *uniformly* even in fresh kidneys is comprehensible, as is also the lack of uniformity among the glomeruli in the action of circulating toxic substances.

A lead may be given concerning the causation of albuminuria under conditions not far removed from the physiological; it is a very old observation that complete arterial interruption of the circulation in the kidney for a short time is followed by albuminuria. If intermittence of glomerular flow is a normal phenomenon it would appear that albuminuria might occur if for any reason the duration of the normal intermittent cessation of flow increased.

I will give the briefest résumé of the chief points presented:

1. New evidence has been secured that increment of blood-pressure, uncomplicated by increment in velocity or volume of blood flow in the kidney, increases urine formation. This is regarded as added support of the filtration hypothesis.

2. Evidence has been secured indicating that some of the most weighty objections to the filtration hypothesis can be reasonably explained in a manner consistent with it.

3. Indications have been shown that nervous stimuli and chemical substances may exert different degrees of effective influence upon the afferent and efferent vessels of the glomerulus and that this may be a factor in that automatic regulatory control of glomerular filtration which is responsible in part for the maintenance of constancy of blood composition.

4. And, finally, a new description of the mode of circulation through the glomerular vessels has been presented which, when verified and extended, we hope will be of service in the study of the normal and pathological physiology of the kidney.

A FURTHER STUDY OF THE QUANTITATIVE VARIATIONS IN THE VIBRATION SENSATION.[1]

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The first contribution to the study of the vibration sensation was made by Rumpf[2] in 1889. A steel tuning-fork was used, and the handle was so made that it was suitable for application of it to the skin surface after the vibration was started. Forks of different rate of vibration were used in this study, as it was found that in different parts of the body different rates of vibration were

[1] Read before the Association of American Physicians, May 11, 1921.
[2] Neurol. Centralbl., 1889, **8**, 185.

better appreciated. Rumpf regarded the procedure merely as a means for the more careful study of skin sensation.

In 1897 Treitel,[3] unaware of Rumpf's work, experimented with a tuning-fork of 128 vibrations, with which the variations in the length of time of the perception of the sensation were studied. He discovered the important fact that under certain pathological conditions tactile sensation and vibration sensation bear a different relation to each other and the one may be altered without alteration of the other. Contrary to the conclusion of Rumpf he decided that the vibration sensation is to be distinguished from a sense of pressure and a sense of touch.

Max Egger is usually regarded as the first to study the vibration sensation. Certainly, he was the first to demonstrate the feasibility of testing the sensibility of bones by means of a tuning-fork. The idea was suggested by the extreme sensitiveness of periosteal lesions. By lifting up a fold of skin in a thin subject and placing it between a vibrating tuning-fork and a fixed object only the very slightest vibration was detected. When the skin was allowed to fall back into place and the instrument was applied it was found that the appreciation was increased tenfold.

Egger[4] demonstrated that this perception of vibration sensation was entirely independent of the presence or absence of cutaneous sensibility. More recently Goldscheider showed that Egger was in error in his conclusion that the vibration sensation is perceived only through bone. He found that the soft parts are susceptible, though not to so marked a degree, owing to the physical property of the tissue. Goldscheider[5] further thought that the observation was dependent in part on the condition of cutaneous sensibility. He experimented with anesthetization of the skin. To test the cutaneous sensibility the instrument was very lightly applied to the skin surface, and to test vibration it was applied much more firmly through the compressed skin. He did not regard it as a specific sensation but as an expression of the sensation of rhythmic interrupted irritation of the nerves that are responsible for the sensation of contact or pressure.

Bing is quite emphatic in stating that through cocain anesthesia tactile, pain and temperature sense may be abolished while the vibration sensation is preserved, and, further, that it is usually not noticeably decreased. He shows many good grounds for the sharp separation of tactile and vibration sensation.

L. F. Barker[6] is disposed to regard the sensation of vibration as due to the result of the stimulation of the touch points in the skin.

[3] Arch. f. Psychiat., 1897, **29**.

[4] Jour. de physiol. et de path. gén., 1899, No. 3, **1**. Rev. neurol., Paris, 1908, **16**, 345–351. Comptes rendus de la soc. de biol., 27 Mai, 1899, p. 423. Comptes rendus de la soc. de neurol., 4 Febr., 1904.

[5] Berl. klin. Wchnschr., 1904, No. 14.

[6] Monographic Medicine, vol. **4**, p. 136.

He says that though this sensation may disappear before there is complete tactile anesthesia, still it seems to indicate that among the earlier disturbances of tactile sensation must be counted an inability to perceive successive impulses of short duration as separate sensations.

In 1903 Rydel and Seiffer[7] gave to the vibration sensation the name pallesthesia, which was a step in the direction of separating it as a different sensation from tactile and other sensations.

For clinical purposes Bing preferred to use the Gradenigo vibrator. A clear description of this instrument is not available. I seems to depend on an optical device as the means of determining a point of fixed amplitude. Barker preferred the C fork of 128 vibrations provided with a Gradenigo triangle on one prong, which permits, he says, of the application of vibrations of very different numbers and the number at the instant of vibration disappearance may be exactly recorded. During the progress of this work various instruments with the Gradenigo triangle were used, but the results did not seem to justify a continuance because of the difficulty in general standardization. It seems justifiable to recall to the reader that a tuning-fork can only vibrate at a fixed rate regardless of the violence of the starting blow. The only thing the blow can alter according to its degree is the amplitude of the vibration or the "degree of swing." To reach some means whereby the amplitude can be standardized is ever the difficulty in perfecting an instrument for quantitative work.

R. T. Williamson,[8] the English pioneer in the study of the vibration sensation in neurology, mentions in his writings the advantages of the Gradenigo instrument. He was impressed with the fact that by it sensation in different parts of the body can be accurately measured. Williamson worked with a C^1 fork nine inches long with prongs five and a half inches long.

In 1911 J. L. M. Symns,[9] working in Guy's Hospital, adopted a tuning-fork for quantitative work which made possible the exact charting in numerical ratio of the responses of the subject in different points on the body surface. The instrument of Symns has a small "window" placed between the prongs at the free ends. If the amplitude is wide enough the prongs separate sufficiently to allow to be seen the two little slots which differ slightly in depth. As soon as the vibration dies out sufficiently the window or slot is covered up. Unless the vibration is quite active the window will not appear. The observer strikes the instrument and then holds it up between his eye and a bright light, preferably a window, and

[7] Arch. f. Psychiat., Berlin, 1903, **37**, 488–536. Neurol. Centralbl., 1903, No. 7. Berl. Ges. f. Psych. u. Nervenkr., 9 Marz, 1903.

[8] British Med. Jour., July 20, 1907.

[9] British Med. Jour., 1912, **1**, 539. Guy's Hospital Reports, 1912, **66**, 120. Quarterly Jour. Med., 1917, **2**, 33–58.

continues to watch the gradually lessening light which is allowed to pass through the slot. At the instant when no more light can be detected the handle of the instrument is applied to the bony point under consideration and the subject told to note the vibration carefully, and at the instant when the vibration is no longer detected to give a suitable signal. The time during which the sensation is felt is recorded in seconds. Symns used a stop-watch, but it is not essential and has the disadvantage of requiring an assistant.

The present work[10] was planned to serve as a continuance of the observations begun by Symns in the same clinic in 1911. Dr. Hurst and Dr. Symns were of the opinion that the normal range established by the latter had been based on too small a number of cases. One hundred normal individuals were studied by me in making a graph of the normal variations. The subjects were bed patients suffering from no nervous disease, willing to coöperate in the test and mentally intelligent. The graph constructed on this series of normal observations varied markedly from that constructed by Symns on a fewer number of observations. This was found to be due to the difference in the two instruments used. Through the help of Mr. H. G. Drew, of Messrs. Down Brothers, Ltd., of London, the makers of the instrument, it was soon learned that while the instrument used in the present work and that used by Symns were both of 108.5 double vibrations per second, and with identical windows the sources of difference could be readily accounted for and in large measure eliminated in future manufacture. Variations in weight and temper of the shaft caused a variation in vibration appreciation. A vibration of 2 mm. swing at the fork end is differently transmitted at the handle end if the rigidity of the fork varies. The instrument used in this work has been carefully weighed and measured by the manufacturer and made the standard. The window, which is really a double slot, has been carefully registered and every precaution will be taken to manufacture instruments conforming to it. It must be remembered, however, that a hand-wrought instrument can never be exactly duplicated, and it is not possible to exactly reproduce temper. It was thought desirable to standardize the instruments in such a way that a normal graph might be supplied with each instrument to facilitate the exact recording of the curve in each individual case.

In the diagrams it will be noted that the observations are made on various bony points of the body and recorded in seconds. The investigation is done in many other ways by a large number of observers. Dr. Henry Head does not use a windowed instrument and does not select the bony points used in the present work. One important part of his examination is timing the period during

[10] Guy's Hospital Reports, January, 1921.

which the vibration can be detected on one side after the vibration can no longer be detected on the other side. That is, he holds the vibrator in contact with a part on the right side until the vibration cannot be felt, then quickly transfers the instrument to the other symmetrical part on the left side and notes the time in which the lessening vibration can be felt. The procedure is then reversed. Dr. Gordon Holmes uses a simple heavy tuning-fork without window and does not make time observations with standardized amplitude. His conclusions are based more on qualitative returns than on quantitative.

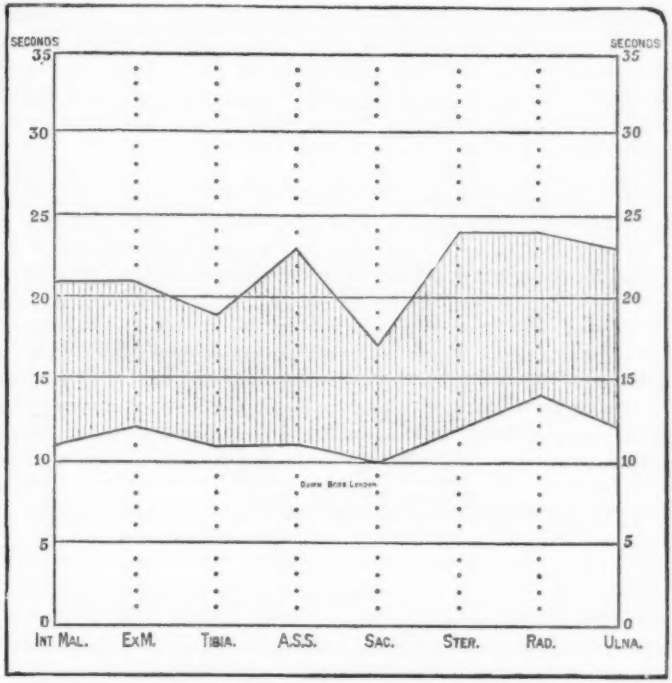

FIG. 1.—Normal range established in 100 non-neurological cases.

It was thought by those interested that the standardization of an instrument with a standard normal range, as has been attempted in this work, might open the way for numerous observations by many observers, resulting in the accumulation of data which is much needed before final acceptance of many of the claims to be made can be expected.

The justification for this present work is the fact that until quantitative variations are appreciated the value of the test is lost

at a time when its aid is most needed. Before total loss of vibration appreciation occurs there is a gradual dimming which with this instrument can be exactly recorded day by day and the progress of the process noted. For example, in tabes dorsalis there occurs late in the disease frequently an entire loss of vibration appreciation in the lower half of the body; but, on the other hand, early in tabes before other signs of recognized value appear it will be found that there is a definite quantitative diminution of the time during which these vibrations of standard amplitude are felt.

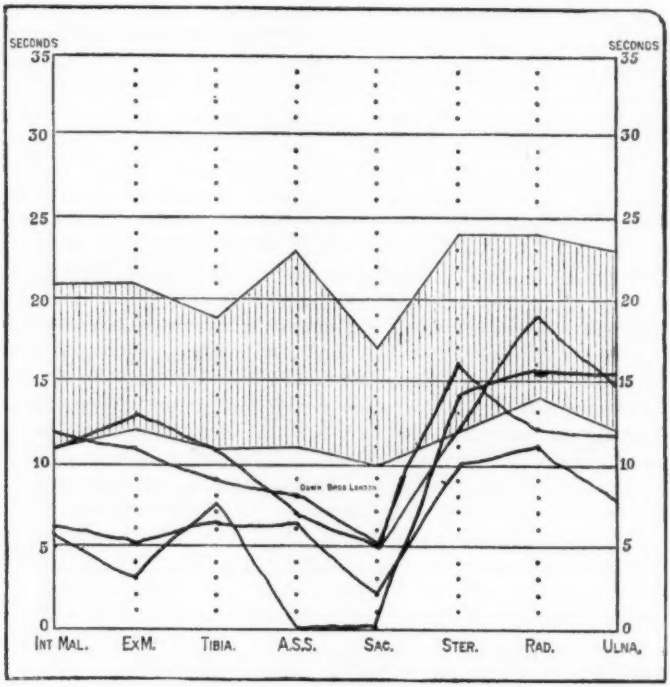

FIG. 2.—Vibration response in 4 cases of tabes.

It is beyond the scope of this article to enter into a discussion of the nature of the vibration sensation and its relation to other sensations. Suffice it to say that under certain pathological conditions of the nervous system there is definite departure from the normal.

The most notable variation of a fixed sort was seen in tabes, as has been mentioned. Eighty cases were studied in various stages, and in large part these cases were kept under prolonged observation watching changes which occur much more markedly in vibration

than in any other sensation. In not one of this series was there an exception to the rule that in the lower half of the body there always occurs a reduction in the time of appreciation of vibrations of a fixed amplitude. This reduction in time was singularly constant in its occurrence over the sacrum. It is rare indeed in any case of tabes, however early, to record a time of more than five seconds over this point. In a large proportion of the cases there was no response at all over this portion of the body. In two or three instances the time recorded was as much as six or even seven seconds. Fig. 2 shows the curves of 4 cases of tabes overlaid. The general tendency to dip at the sacrum is well illustrated. In many instances this low response or absence of response occurs when the instrument is applied to the anterior-superior spines of the ilia. It is exceptional for the curve in tabes to fail to fall within the normal range in the upper extremity, and in some instances there is really a high response in this part of the body. This is one of the distinctive differences between tabes and multiple neuritis. In the latter the normal range is seldom encroached on at any point and the "sacral dip" is absent.

This study has led to the conclusion that loss of vibration appreciation is the first sensory loss in tabes. This is illustrated in a man studied in the Addison Ward, Guy's Hospital, whose diagnosis was thoracic aneurysm. The blood in this case was Wassermann negative while the spinal fluid was strongly positive. There were no disturbances of tendon reflexes; the pupils were negative and careful study of skin sensation failed to reveal any areas of analgesia. The curve represented in Fig. 3 shows a low vibration response. It will be noted that the loss is not total but merely a quantitative change which would be readily overlooked were the investigation merely qualitative. This patient was held in the hospital over a long period, and we had the satisfaction before his discharge of seeing the development of areas of analgesia over the tibiæ. It seemed justifiable after a study of a number of such cases to conclude that analgesia followed the alteration of vibration response. In many instances the finding of a low vibration response prompted a careful study of the whole body surface, with the result that certain areas of analgesia were sometimes found. In Fig. 4 the patient, whose reflexes were preserved, showed no appreciation of pain when a pin was plunged into the tip of his nose deep enough to hold it in position. Vague gastric cases in which pain was the predominating factor, studied by the vibration test, proved the usefulness of the procedure. In some clinics gastric crisis as a very early symptom of tabes is frequently noted. Why there should be a difference in this observation in different places is not readily understood. In collecting the normal hundred on which the normal range was established gastric cases were sought after because of the non-neurological character. This opened up a most

interesting field, for it was found that in a number of instances these cases showed extraordinary abnormalities in the vibration response. In one case a tentative diagnosis of carcinoma had been made by a very capable house physician. Study of the nervous system showed gastric crisis in early tabes. In another case in the same ward ulcer had been diagnosed and the patient had been on rigid treatment for some time. Vibration study

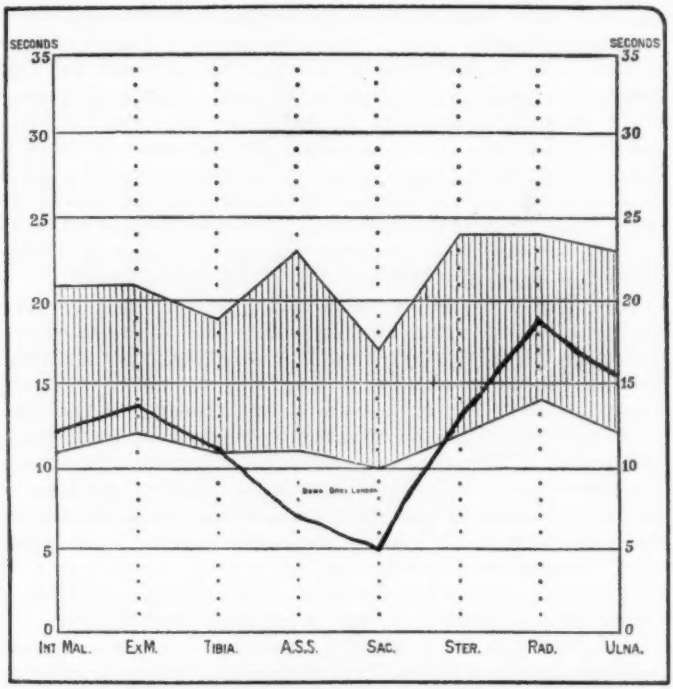

FIG. 3.—Man, aged fifty-five years. Admitted to Guy's hospital (Addison Ward) for aneurysm. The blood was Wassermann negative but the spinal fluid was strongly positive. The vibration curve was that of tabes, and he was kept in the hospital until other signs developed sufficient for a confirmation of this diagnosis. (Guy's Hospital Reports, January 1921).

opened the way for a correction of the diagnosis, which was clearly gastric crisis in early tabes. Recently a case was studied in which the vibration response was distinctly that of tabes. Gastric pain was the symptom, and a most careful chemical and fluoroscopic study had been made. The tendon reflexes were preserved and there was no Argyll Robertson pupil, though the pupils were contracted. Analgesia of the skin of the face as well as other scattered areas suggested tabes, which was verified by spinal puncture. In

still another case now under observation the diagnosis of carcinoma seemed well justified, but vibration suggested tabes, which was borne out by the Wassermann test and cell count of the spinal fluid.

In the 80 cases studied there has not occurred a single instance in which there was not a definite time reduction in vibration response, which usually manifested itself in the form of the "sacral dip." In this other points of the lower half of the body frequently shared. It can be safely stated that any case with no

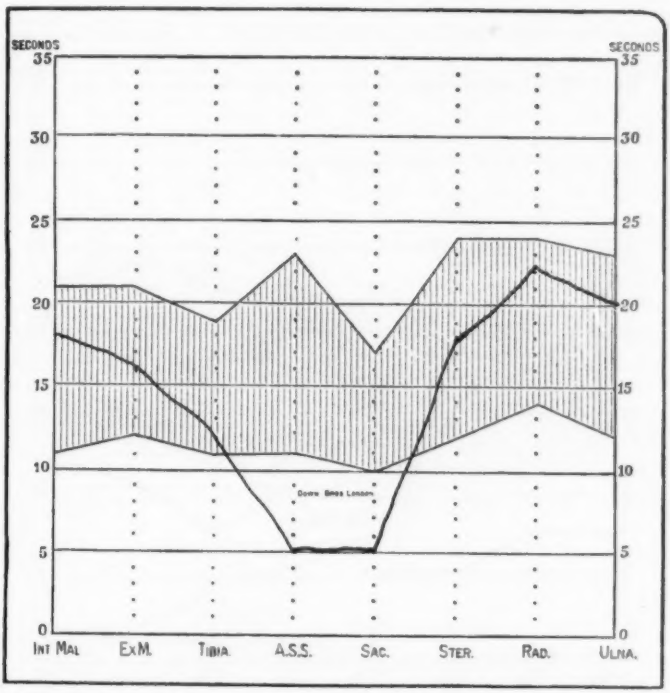

FIG. 4.—Tendon reflexes preserved. Marked analgesia of the skin of the face.

reduction in the time of vibration response over the sacrum is not tabes, an observation which can be easily made in one-half a minute and relied upon without further investigation.

In multiple neuritis there was noted decided reduction in the vibration time. The distinctive "sacral dip or the notch," so marked in tabes, did not occur in any case. There was a general reduction of the time, but a tendency for the sacral point to be relatively high and in many cases higher than the other points. In addition to this there was usually absent that tendency so

marked in tabes for the time response of the upper extremity to be normal, making a curve which in that part of the body falls well within the normal range. In diabetes it was interesting to record the improvement in sensation indicated by the vibration curve in those cases receiving proper dietetic treatment. In a case of multiple neuritis occurring in a woman who was a victim of pellagra, seen in the service of Dr. Edwin Bramwell, in the Royal Infirmary, Edinburgh, there was this definite reduction in vibration time with the high point over the sacrum. It was notable in

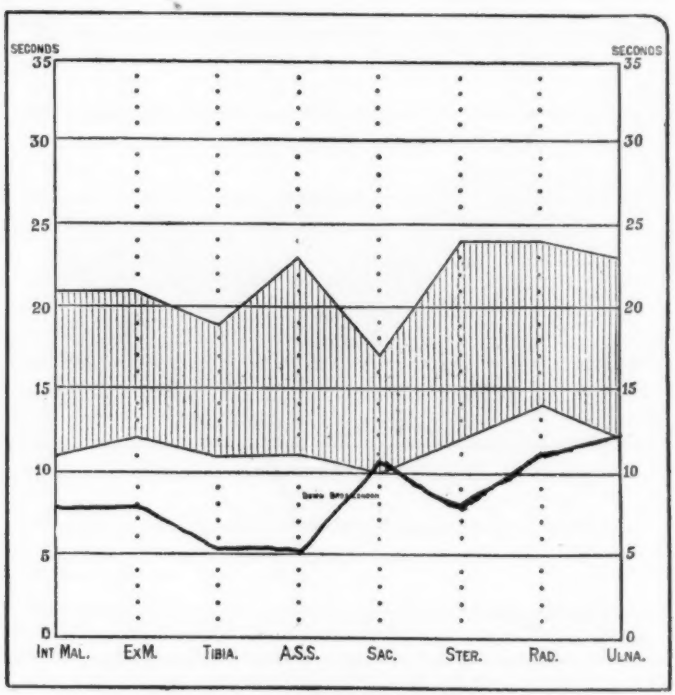

FIG. 5.—Multiple neuritis in pellagra.

this case that pain and tactile sensations were not disturbed and temperature sense only slightly. The vibration time is recorded in Fig. 5.

Three cases of Friedreich's ataxia were studied in Guy's Hospital and showed a loss in the vibration time quite like the changes noted in early tabes. The loss of vibratory appreciation was not complete, and would have been overlooked if a qualitative test alone had been made. As in tabes there is a "sacral notch" in the curve of these cases.

Subacute combined degeneration of the spinal cord in association with pernicious anemia was studied in 5 cases. In all cases there was a definite loss of the vibration response which, until late in the process, was confined to the lower half of the body, with little abnormality in the upper half. In 1 of these cases the loss was complete in the feet; marked over the tibiæ, but not entirely lost; less over the anterior-superior spines and still less over the sacrum, with a gradual ascent in the upper portion of the body. This is seen in Fig. 6, which is made of 2 such cases.

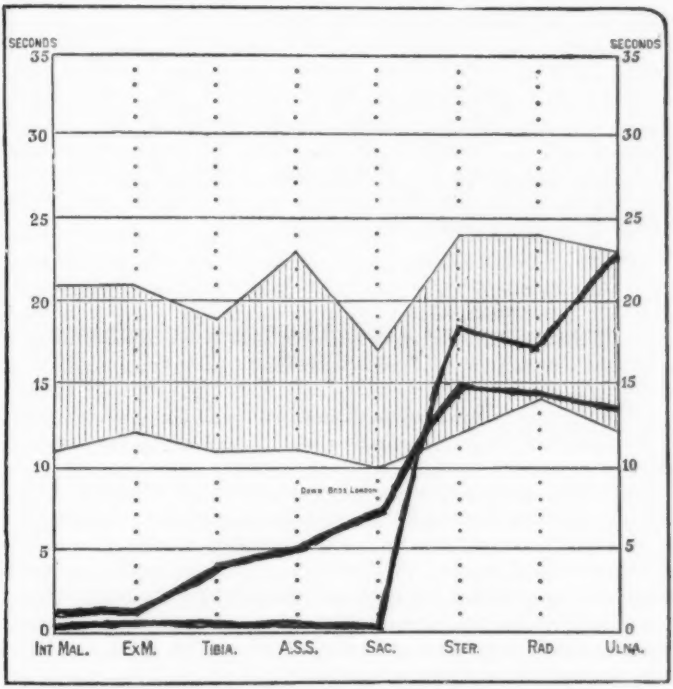

FIG. 6.—Two cases of subacute combined degeneration of the cord in pernicious anemia.

In all of these cases the "sacral notch" of tabes was not pronounced. The curve can be readily distinguished from that of multiple neuritis.

One case studied caused much confusion because the response over the sacrum was entirely absent while the blood and spinal fluid were negative to the Wassermann reaction. Incontinence of bowel and bladder were present. Study of skin sensation about the anus and down the lower limbs gave the characteristic findings of a lesion of the cauda equina.

One of the most fertile fields for the study of the vibration sensation is syphilitic meningomyelitis. In this condition the vibration response was found to be reduced in the lower half of the body, but there was more evidence of asymmetry than is usually noted in such cord lesions as tabes. The great helpfulness of the test seems to be in gauging improvement. It seems probable that an improvement in the spinal fluid will run more or less parallel with an improvement in sensation, and this may be measured in a quantitative way by using the vibration sensation. A beginning only has been made in this work which requires much time and very exact laboratory work by an expert serologist.

In conclusion, I would express my thanks to Dr. A. F. Hurst, of Guy's Hospital, under whom the work was done for aid of every sort; to Dr. Gordon Holmes, for suggestions and clinical opportunities at the National Hospital, Queen Square, at Charing Cross Hospital and at Moorfields; to Dr. Edwin Bramwell, for material and much aid at the Royal Infirmary, Edinburgh; to Sir James Mackenzie, for an opportunity to do further work at the Clinical Institute of St. Andrews, Scotland.

PERIPHERAL AND RADICULAR TYPES OF EPIDEMIC ENCEPHALITIS.[1]

By Foster Kennedy, M.D.,
NEW YORK.

It is only for the purpose of presentation of different clinical aspects of epidemic encephalitis by different observers that we have in this conference divided with some arbitrariness the disease into different clinical groups. A clinical discussion under these circumstances therefore must begin by a disclaimer that the type assigned to each author is ever a disease of its own genus, and by an assertion that it merely represents a variety in which the virus has fallen with some greater incidence on one part of the body than on another. Of the circumstances which go to permit this variety of form we know little: naturally, disease pictures will vary with the structure affected and variety in such pictures following nervous lesions is furthered because from lesions of the nervous system we may have either obliteration of normal function or release of functions normally controlled by centers higher in the neural hierarchy.

It is probable that variety of clinical form in epidemic encephalitis is also often produced by variety of virus or by a constant virus

[1] Read before the Association for Research in Nervous and Mental Diseases, December 29, 1920.

varied by appearing in different evolutionary guises. However this may be it is certain that the peripheral nerves and spinal roots are affected in encephalitis to a considerable degree. Abrahamson says that in 60 per cent of his cases unmistakable signs of radiculitis were present. This is a higher figure than has been obtained in our series at Bellevue Hospital; we have been slow, however, to ascribe to root or peripheral infection subjective symptoms unsupported by objective phenomena; nevertheless, in some cases the distribution and character of the pains have forced us to the same conclusion; in a few others, sensory changes similar to those found in tabes dorsalis have been present; in a small number there have been localized atrophies of muscles such as would occur from involvement of contiguous anterior roots. Palsies of single cranial nerves are not uncommon, the seventh and third nerves being those most usually affected. It should be pointed out that the involvement of the seventh nerve in most of our cases has not been accompanied by any defect either of the fifth, eighth or sixth nerves, a consideration which would exclude the possibility of the lesion being in the pontocerebellar angle or in the nucleus of the facial nerve in the pons, and would compel observers to explain the facial palsies in these cases by a lesion of the seventh nerve in its parenchyma. Not only were single cranial nerves picked out for damage by the infection, but occasionally single peripheral nerve trunks were involved in similar fashion. An interesting example of this was seen in a riveter who in April, 1920, began suddenly to have sharp lancinating pains in the arms and shoulders accompanied by much weakness in the upper extremities. When examined, some three weeks after the beginning of these symptoms, he was found to have a noticeable loss of power in both serratus magnus muscles, the right scapula being winged on raising the arm on that side. The patient had diplopia, heavy sweating, slowness of emotional initiative and a mask-like facies some four weeks after the development of his peripheral nerve symptoms. It is at least an interesting speculation whether this man's occupation as a riveter, imposing reiterated violent exertion of his serrati and notably of the right muscle, could have had any determining effect on the incidence of the disease on the long thoracic nerve.

Several observers, notably Pardee and Barker, have described cases of severe girdling pains beginning in the cervical region, with persistent hiccough and descending to the lumbar region and lower extremities. None of their cases had any objective sensory losses, but all had a pleocytosis in the spinal fluid. It is remarkable that more such patients had not herpetic manifestations; only one of the Bellevue group had herpes, and that was confined to the left auricle and external auditory canal, and was associated with a complete left facial palsy of a peripheral type; a geniculate ganglionitis was in this case the presumptive lesion.

The prognosis in the peripheral and radicular varieties of this disease is good, a happy stiuation which unhappily prevents pathological confirmation of clinical diagnosis. However, in cases fatal through cerebral involvement there have been found in the posterior root ganglia by Strauss and Loewe and by Flexner and Amoss perivascular round-cell infiltrations and occasional hemorrhages.

It is not necessary to describe the details of cases such as have been mentioned, but instances of indubitable polyneuritis on an encephalitic basis are less common in the experience of the workers in Bellevue Hospital and the Neurological Institute than are the radicular types or those in which isolated nerve trunks such as the facial are alone involved.

J. D., a watchman, aged fifty-three years, formerly a coachman, a man who had never drunk more than an occasional glass of beer, in August, 1920, began to suffer from severe burning pains in the calf muscles, with tingling in the toes and progressive weakness in the legs. He became unable to walk and at the same time had severe headaches and felt very ill. He had a constant pyrexia of about 2° F. After two weeks the same symptoms as had been in the legs were felt in the arms, which gradually weakened. A month after these developments he began to see double, his pupils became unequal and sluggish to light, the left face became weakened, the facial expression grew masklike, he sweated excessively; the sleep mechanism was reversed—that is, he was drowsy by day and wide-awake by night—the pulse was persistently about 125 and the sugar content of the spinal fluid and its cell content were greatly increased. There was atrophy in the intrinsic muscles of both hands and fibrillary twitching in all four limbs. All deep reflexes were abolished. There was excruciating tenderness in the calf muscles and abolition of the sense of position in the feet and hands, with consequent sensory ataxia. There was no weakness in speech or swallowing. Micturition was slow and difficult, but there was no incontinence. This patient is making a slow recovery (December, 1920).

This case and two others in the neurological department at Bellevue Hospital remarkably resembled those reported before the American Neurological Association by myself under the caption "Acute Infective Neuronitis." In them, however, it was unusual to have a cerebral symptom-complex, though autopsy examination revealed inflammatory lesions in the peripheral nerves, spinal ganglia and cord and cortex as well—lesions which for the most part, however, diminished as one ascended in one's examination.

These cases occurred as a minor epidemic among soldiers in the field; they had fever and other evidences of a general infection. In some few the posterior spinal roots were especially affected, so that root zones of grossly altered sensibility were easily demon-

strated. A constant feature of these soldiers was the peripheral paralysis of one or both sides of the face—a feature commonly but by no means constantly seen in the American cases of epidemic encephalitis.

In connection with these cases, however, we must consider those of acute polyneuritis occurring as a complication of malaria and of enteric fever and scurvy, and perhaps especially those recently described by Farnell in which a staphylococcal gastro-enteritis was promptly followed by acute polyneuritic symptoms with not infrequently fatal results. All these diseases differ from similar conditions found in the encephalitic epidemic in degree rather than in type, but make manifest that disease pictures are sketched and colored more by the varying natures of the structures attacked than by the specificity of the invading virus.

FURTHER OBSERVATIONS ON THE BLOOD-SUGAR TOLERANCE TEST AS AN AID IN THE DIAGNOSIS OF GASTRO-INTESTINAL CANCER.[1]

By Julius Friedenwald, M.D.,

and

George H. Grove, M.D.,

Baltimore, Md.

In a study of the blood-sugar tolerance test as an aid in the diagnosis of gastro-intestinal cancer presented by us last year the following conclusions were noted.

1. There is present in carcinoma of the gastro-intestinal tract usually a rather characteristic curve of sugar tolerance which differs somewhat from that observed in carcinoma of other regions of the body. The curve of this affection usually presents a high sugar content even in the fasting state followed by an initial rise up to 0.23 per cent or higher within forty-five minutes after the ingestion of the dextrose remaining at this level for at least two hours, and rarely at any time during this period falling below 0.2 per cent.

2. The sugar-tolerance test is rather distinctive, so that it may render valuable assistance as a means of differential diagnosis between carcinoma and other diseases of the gastro-intestinal tract.

3. The opportunity has not been afforded to test a sufficient number of early cases of cancer of the stomach and intestines according to this method, so that as yet the value of this test as a means of early diagnosis has not been established; nevertheless, as

[1] Read at the Meeting of the Association of American Physicians, Atlantic City, May 11, 1921.

positive curves occur equally whether cachexia exists or not, or whether the extent of the involvement be slight or great, we are under the impression that the results may be quite definite even in the early cases of the disease. This question, however, requires further study.

4. While we fully realize that this test is not specific of carcinoma and cannot be relied upon alone without entering into the clinical aspects of the disease, and that there are cases of carcinoma in which negative findings occur or non-malignant conditions in which the results are positive, nevertheless we are of the opinion that when properly performed the blood-sugar tolerance test may be of considerable diagnostic help in obscure cases of carcinoma of the gastro-intestinal tract.

At that time our study included 32 cases of cancer of the gastro-intestinal tract, all of which presented the typical cancer curve. This curve was, however, not observed in any one of 55 other examinations, including 5 cases of carcinoma outside of this tract nor in 45 cases of benign affections of the gastro-intestinal tract, including peptic ulcer, syphilis of the stomach, diarrhea, dysentery, achylia gastrica, chronic gastritis, cholelithiasis, chronic appendicitis, enteroptosis, nervous dyspepsia and mucus colitis.

The typical cancer curve can easily be distinguished from that observed in other affections of the gastro-intestinal tract. It must be differentiated according to our observations from the normal curve, the atypical curve and the intermediate curve.

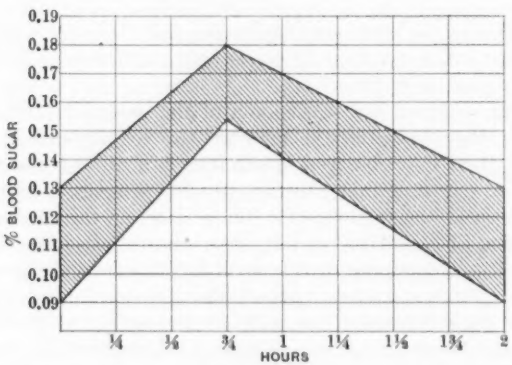

CHART I.—Maximum, minimum and average normal blood-sugar tolerance curve.

The Normal Curve. In normal individuals after the ingestion of 100 gm. of dextrose the blood-sugar content rises from 0.09 or even less to a height not usually above 0.165 per cent within forty-five minutes, falling usually more gradually within two hours to about the level as that observed in the fasting state. This character of

curve was observed not only in normal individuals but also in the non-cancerous digestive disturbances other than those which have been classified in the following groups.

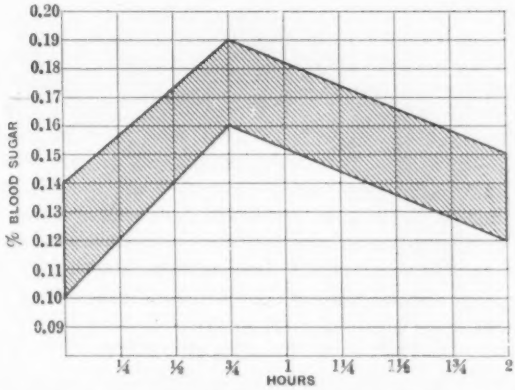

CHART II.—Maximum, minimum and average atypical normal curve.

The Atypical Normal Curve. In certain individuals, often those affected with an achylia gastrica, an atypical normal curve is observed in which the blood-sugar content presents practically normal values in the fasting state, ascending to a height of from 0.16 to 0.18 per cent within forty-five minutes after the ingestion of the dextrose, falling slowly within two hours to a level of from 0.13 to 0.15 per cent, but not any lower.

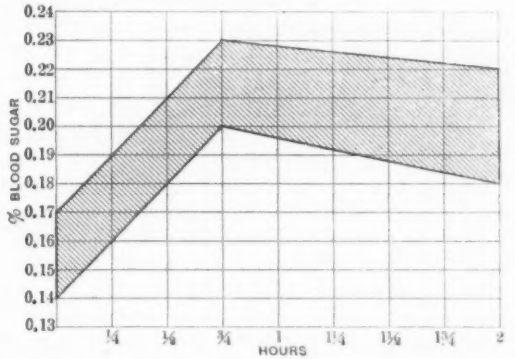

CHART III.—Maximum, minimum and average intermediate blood-sugar curve

The Intermediate Curve. The intermediate curve is usually observed in cases of carcinoma not associated with the gastro-

intestinal tract, in which the blood-sugar content presents comparatively high values even in the fasting state of 0.14 to 0.17 per cent,

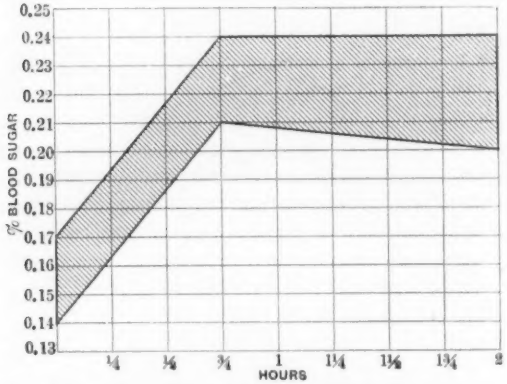

CHART IV.—Maximum, minimum and average blood-sugar tolerance curve in carcinoma of the gastro-intestinal tract.

and in which after the ingestion of 100 gm. of dextrose there is an initial rise to a height of from 0.2 to 0.23 per cent within forty-five

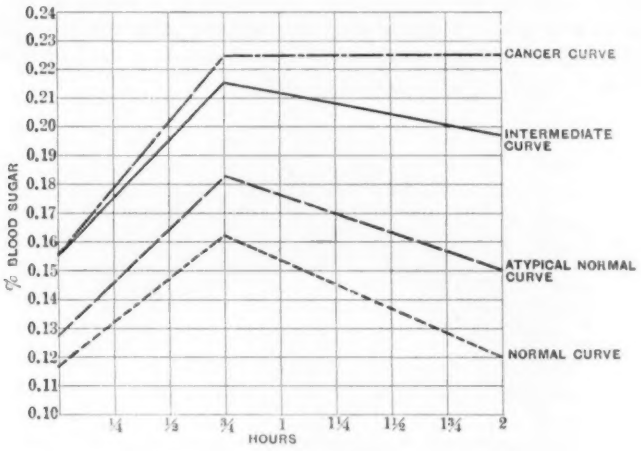

CHART V.

minutes, followed within two hours by a fall of from 0.18 to 0.21 per cent, never descending at this time to the level observed in the fasting state.

Since our former publication we have examined 43 additional cases of gastro-intestinal cancer, according to our method, totalling in all 75 cases. All were typical of the disease; of these 36 were operated on and the diagnosis was thus confirmed, and in the remaining cases there were definite palpable abdominal masses in addition to the usual physical signs present in this affection, and the examination of the gastric contents as well as the roentgen-ray findings and final outcome presented confirmatory evidence in every instance. Of these cases there were 47 of gastric carcinoma, of which there were 5 of cancer of the esophagus and cardia, 26 with obstructions at the pylorus, while 16 presented no obstruction. There were 5 cases of cancer of the colon, 2 of the pancreas, 8 of the liver, including 5 other abdominal organs; 3 of the rectum and 11 cases of carcinomatosis and 1 of the face and tongue.

In our examinations we followed the plan described in our former communication with the patient on a fasting stomach; blood was withdrawn for examination just before; in forty-five minutes; and two hours after the administration of 100 gm. of dextrose and the blood sugar determined by means of the Epstein method under the identical precautions described by us.

The character of curve present under these conditions in gastro-intestinal cancer is quite characteristic and can usually be distinguished from that observed in cancer of any other region of the body or from that in non-malignant diseases. It was noted in all of these cases of cancer of the gastro-intestinal tract but 3, of these 2 G. D. (No. 15) and M. P. M. (No. 50), were instances of general carcinomatosis and 1, C. I. (No. 33), a case of rectal carcinoma; in all the diagnosis was confirmed by operation and the curves presented were typically normal.

On the other hand there were 5 cases proved by operation to be non-malignant in which typical cancer curves were obtained; of these there was M. B. C., a case of tuberculous peritonitis; M. M. C., of gastric syphilis; B. H., of carcinomatosis; S. O., of cholelithiasis, and J. T. S., of gastric syphilis.

It is important to note that diabetes, nephritis, tuberculosis and disturbances of the thyroid should always be excluded before the tolerance test is undertaken, inasmuch as hyperglycemia is frequently present in these affections. However, as this test is to be utilized only as a means of differentiation between carcinoma and other diseases of the gastro-intestinal tract many conditions associated with hyperglycemia need not here be taken into consideration.

Inasmuch, therefore, as this test has proved positive in 72 of the 75 cases of cancer of the gastro-intestinal tract, there can be but little question of its value as a diagnostic measure even though it was found positive in 5 cases of non-malignant disease of these organs.

TABLE PRESENTING THE PERCENTAGES OF BLOOD-SUGAR OBTAINED IN SEVENTY-FIVE CASES OF CANCER OF THE GASTRO-INTESTINAL TRACT.

1.	A., F. C.	Cardia	.172	.260	.248
2.	B., C.	Pylorus	.164	.224	.230
3.	B., C.	Cardia	.192	.282	.250
4.	B., C.	Stomach	.141	.193	.172
5.	B., C.	Stomach	.140	.193	.172
6.	B., I.	Pylorus	.121	.197	.178
7.	B., B.	Pancreas	.159	.194	.198
8.	B., M. J.	Pylorus	.141	.250	.238
9.	B., G. F.	Liver	.120	.198	.192
10.	B., S. S.	Stomach	.163	.268	.278
11.	C., M. H.	Stomach	.196	.240	.243
12.	C., M.	Stomach and liver	.146	.230	.242
13.	C., T.	Stomach and liver	.147	.194	.191
14.	C., G.	Stomach	.162	.204	.201
15.	D., G.	Carcinomatosis	.142	.180	.150
16.	D., B.	Carcinomatosis	.156	.260	.268
17.	D., N.	Stomach	.170	.220	.224
18.	D., J. A.	Carcinomatosis	.161	.258	.255
19.	D., C. E.	Pylorus	.131	.187	.183
20.	D., D. E.	Stomach	.178	.364	.332
21.	F., S.	Rectum—before operation	.198	.198	.200
		after operation	.148	.188	.184
22.	F., M.	Liver	.120	.180	.200
23.	F., T. W.	Pylorus	.154	.226	.272
24.	G., M.	Carcinomatosis	.150	.186	.190
25.	G., E.	Intestines and uterus	.125	.187	.194
26.	G., D.	Carcinomatosis	.161	.250	.256
27.	G., H.	Liver	.163	.214	.208
28.	H., C.	Pylorus	.147	.192	.188
29.	H., I. L.	Liver	.154	.210	.206
30.	H., S.	Rectum and intestines	.172	.248	.280
31.	H., W.	Pylorus	.149	.198	.194
32.	I., C. S.	Cecum—before operation	.155	.226	.258
		after operation	.082	.170	.110
33.	I., C.	Rectum	.120	.167	.113
34.	J., P.	Pylorus	.142	.187	.179
35.	K., W. H.	Pylorus	.176	.282	.270
36.	K., B.	Pylorus	.132	.198	.214
37.	L., J.	Stomach	.148	.236	.232
38.	L., J. E.	Stomach	.198	.276	.264
39.	L., M. B.	Pylorus	.159	.191	.198
40.	L., F. C.	Stomach	.170	.268	.208
41.	L., F.	Rectum	.202	.300	.264
42.	L., J.	Pylorus	.176	.252	.266
43.	M., F.	Liver	.154	.200	.204
44.	M., R. E.	Stomach	.142	.194	.192
45.	M., P. J.	Pylorus	.116	.206	.192
46.	M., J.	Prostate and intestines	.157	.198	.172
47.	M., C. J.	Carcinomatosis	.158	.210	.210
48.	M., M.	Pylorus	.138	.204	.204
49.	M., H. T.	Pylorus	.136	.252	.280
50.	M., M. P.	Carcinomatosis	.120	.168	.127
51.	N., A.	Intestines	.154	.216	.220
52.	P., G. C.	Stomach	.164	.242	.238
53.	P., L.	Cardia	.168	.204	.192
54.	P., M. G.	Stomach	.152	.198	.200
55.	P., T.	Carcinomatosis	.171	.234	.242
56.	P., H. G.	Stomach	.142	.262	.247

57.	R., E.	Pylorus	.141	.192	.174
58.	S., E. P.	Bladder and liver	.160	.245	.238
59.	S., F. L.	Tongue	.384	.497	.497
60.	S., C.	Carcinomatosis and liver	.162	.198	.200
61.	S., I. P.	Carcinomatosis	.121	.162	.153
62.	S., M.	Cardia	.131	.180	.224
63.	S., C.	Stomach	.206	.266	.256
64.	S., L.	Cardia	.178	.234	.228
65.	T., J. T.	Pylorus	.171	.239	.240
66.	T., M.	Carcinomatosis	.171	.214	.204
67.	V., S.	Stomach	.138	.214	.206
68.	W., C.	Pancreas	.160	.224	.198
69.	W., C. C.	Pylorus	.156	.230	.218
70.	W., L. H.	Stomach	.168	.290	.270
71.	W., S.	Pylorus	.162	.198	.194
72.	W., E.	Stomach	.154	.192	.178
73.	W., V.	Pylorus	.164	.198	.224
74.	Z., V.	Pylorus	.152	.236	.240
75.	Z., W. A.	Pylorus	.161	.220	.218

The value of this test is well illustrated in 3 cases of this series. We append a brief abstract of the histories of these cases.

CASE I.—S. B. (No. 2112), female, aged sixty-seven years, had been complaining of digestive disturbances for many years. Her appendix had been removed in 1908 with marked relief, but during the following year symptoms were again noted in the form of acute attacks of pain in the upper right quadrant, which were severe at times and were accompanied by nausea, vomiting, chills and fever, but without jaundice. Recently the attacks had become more frequent, but not quite so severe as formerly, though during the past two weeks there was continuous distress in the abdomen accompanied with nausea and vomiting. Loss of flesh and great prostration were also noted. At this time the liver had become markedly enlarged and quite tender on pressure. The diagnosis of cholecystitis was made even though the blood-sugar tolerance test revealed a typical cancer curve. At operation numerous adhesions were detected in the upper right quadrant region and the gall-bladder was found to contain a thickened, ropy, infected bile, and cholecystectomy was performed. The patient recovered from the effects of the operation, but after several weeks nausea, vomiting and abdominal discomfort manifested themselves. Symptoms of pyloric obstruction were now noted with vomiting of the retention type. A month following the first operation a second was performed for the relief of the pyloric obstruction, when a large carcinoma was observed involving the pylorus and liver.

CASE II.—C. S. I. (No. 5091), male, aged fifty-four years, had been affected with indigestion for four months. At the onset he was taken with an acute attack of pain in the lower right quadrant of the abdomen and a diagnosis of acute appendicitis was made; since then there had been constant indigestion, with general discomfort in the abdomen, pressure, distention, loss of appetite,

eructations, extreme constipation and a loss of thirty pounds in weight. On palpation a mass was noted in the right lower quadrant with extreme tenderness in this area. The blood-sugar tolerance test revealed a definite cancer curve. At operation, performed by Dr. J. M. T. Finney, a carcinoma of the cecum was revealed and resection was performed; no metastases were noted. The patient made a good recovery, and when a subsequent blood-sugar tolerance test was made two months after operation a perfectly normal curve was revealed.

CASE III.—J. S. L. (No. 22677), female, aged sixty-six years, had been affected with abdominal pain and indigestion for some months, which had become aggravated during the past few weeks. There was pain in the right lower quadrant which was dull and dragging in nature, gradually becoming more and more intense; finally exquisite tenderness was noted in the region of the abdomen and the diagnosis of ovarian cyst with possible twisted pedicle was made. At operation on entering the abdominal wall an enormous pocket of pus was found from which a liter of pus exuded and a retrocecal abscess was dicovered. A blood-sugar tolerance test made at this time revealed a typical cancer curve. The patient continued with abdominal discomfort and slight temperature notwithstanding the free drainage; nausea, vomiting, progressive weakness and loss of flesh became prominent manifestations. The drainage continued, and when a larger incision was made carcinomatous infiltration of the intestine and peritoneum was observed.

Conclusion. From our further study of the blood-sugar tolerance test in malignant as well as in benign diseases of the gastro-intestinal tract we are more fully convinced that this test may be utilized to great advantage as a means of differentiating between these affections, and that while it cannot in any way be considered specific for carcinoma, when taken into consideration with the other clinical evidence it may serve as a valuable aid in diagnosis in obscure cases of carcinoma of the gastro-intestinal tract.

SYMPTOMS OF APPENDICITIS IN ACUTE PERICARDITIS.

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AND

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IT is a frequent experience to have pain, tenderness and resistance in the right iliac fossa in cases of pneumonia. It unfortunately

too frequently happens that an operation for appendicitis is done when the only lesion is a pneumonia or a simple severe pleurisy. It is rare to have the same symptoms in pericarditis.

The writers have seen three cases of acute pericarditis in children: one with a purulent exudate, and the other two apparently without pericardial effusion, which were positively diagnosed appendicitis. In one of these an operation was ordered, but was not performed.

CASE I.—M. S., aged twelve years, was seen in consultation with Dr. Devitt, Manayunk, Philadelphia.

She was known to have cardiac disease. This proved to be both endocarditis and pericarditis. On the third or fourth day of her illness she developed severe abdominal pain referred to her right iliac fossa. At the same time her fever increased, her pulse became more rapid and a supervening appendicitis was suspected.

On physical examination a distinct pericardial friction was discovered, accompanied by a loud mitral systolic murmur.

Her whole abdomen was tense and tender. Over McBurney's point there was more tenderness and resistance than over any other portion of the abdomen. On account of the primary occurrence of the pericarditis and the rapid disappearance of appendicular symptoms as the pericardial symptoms disappeared the case was diagnosed as one of pericarditis and endocarditis, with pain referred to the right iliac fossa. The patient made an excellent recovery; the appendicular symptoms never reappeared.

CASE II.—A. T., aged five years, sent by Dr. A., was admitted to the children's ward at the Protestant Episcopal Hospital of Philadelphia November 7, 1920, with a diagnosis of appendicitis.

The family and personal history were negative.

History of Present Illness. The chief complaint was pain in the abdomen radiating to the chest. On October 28, 1920, the patient complained of pain in one leg and then in the other leg. On October 25 or 26 pain in the abdomen developed. The child became nauseated and had several bowel movements, composed principally of mucus, and was sent to the hospital with a diagnosis of appendicitis.

Examination. Well-nourished boy with slight pallor. The lungs are normal. There is a well-marked pericardial friction over the upper portion of the cardiac area. The cardiac area is not increased. At the time of admission there were abdominal symptoms and pain in the right iliac fossa. No other sign of appendicitis occurred during his stay in the hospital. His urine was normal. The leukocyte count was 18,800. He entirely recovered and was discharged December 4, 1920.

CASE III.—M. B., aged seven years. Father and mother living and well. Four brothers dead: one of diphtheria, one of meningitis

and one was stillborn. Four died of gastroenteritis. No other boys are living. One sister living, none dead. The patient was admitted to the children's ward of the Protestant Episcopal Hospital November 7, 1920.

Personal History. Had measles and whooping-cough five years ago. Two months ago had an attack of acute rheumatism and one month later had tonsillitis. No other illnesses. No operation or injuries.

Present Illness. The chief complaint was pain in the abdomen. Began about three days ago with fever and vomiting, but when it began there was no pain in the abdomen. On the second day his condition continued the same; the child was more feverish and complained somewhat of shortness of breath. On the third night he began to complain of pain in the abdomen. The mother does not know whether pain was localized or diffuse. Vomiting continued. The mother stated that the child had vomited twenty times during the day. The bowels moved four times during the fourth day.

Examination. The patient was a well-developed young child. Had rapid breathing, with the face slightly flushed, and a short cough. Head negative, face congested and teeth in fair condition. Breath sounds are lessened over the left lower lobe laterally. Heart shows a very loud mitral murmur. The abdomen seems tender on both sides. No rigidity.

The pulse is rapid; the precordia is bulging. The abdomen is normal in shape. The cardiac impulse is diffuse over the precordia; the apex-beat is at the upper line of the fifth interspace. Heart dulness extends to the midline of the sternum, to the anterior axillary line and apparently runs up to both clavicles. Higher pitched note over the left clavicle than over the right. Typical pericardial friction is heard. A systolic murmur also is heard in the mitral area. Breath sounds are much louder in the left axilla than in the right, in addition to what appears to be a pericardial friction rub and a pleuropericardial murmur heard at the angle of the left scapula. The lungs are apparently normal. No tubular breathing and no bronchophony. The abdomen is resistant, distended and tender. There is most marked tenderness and resistance in the region of the appendix. So great and prominent are the appendicular signs that the surgeon in consultation made a diagnosis of appendicitis. Peristalsis is present.

February 4, 1920. Friction is evident and superficial. Tubular breathing posteriorly over the left chest at the angle of the scapula. Vocal fremitus is increased.

February 5. The abdomen is soft; no pain. All the abdominal symptoms have disappeared.

February 8. Blowing breathing at the angle of the left scapula still continues. There are no signs of abdominal distention today. Pericardial friction is still evident.

February 9. Dulness over the right edge of the sternum at the

upper border of the second rib, just outside of the nipple line. Still area of dulness at the angle of the scapula. Still blowing breathing and bronchophony.

February 11. Pulse is rapid and feeble. Friction sound is evident in front. Dulness in the right axilla. Blowing over practically the whole base posteriorly.

February 13. Tap of the pericardium in Rotch's notch positive today and 35 cc of fluid were removed. Heart dulness is to the right of the sternum in the axillary line. Heart action still rapid. Friction still present; not as much blowing as yesterday. Still marked blowing at the angle of the scapula.

February 14. Patient's condition is much worse. Breathing is more labored; pulse is imperceptible; face is pale. Cyanosis around the lips. Rales in the chest. Heart sounds indistinct.

At 3.30 P.M. the patient's condition is unimproved. Died at 5.20 P.M.

Autopsy. The heart was found to be enlarged. There was no fluid in the pericardium; there was a typical "butter-fat" appearance of the exudate in the pericardium. The pericardium was adherent to the lung posteriorly. The appendix was normal and there was no evidence of past or present inflammatory condition.

Recently the senior author saw a case with typical symptoms and physical signs of a large pericardial effusion.

Two weeks previously the patient had been seized with abdominal symptoms significant of appendicitis. An operation was performed. According to the operator the appendix was mildly inflamed, with some lymph on its exterior surface. Immediately after the operation the child developed a well-marked pericarditis. Here, then, is a case in which a pericarditis was coexistent with appendicitis, showing that care must be exercised in differentiation, bearing in mind that an appendicitis and pericarditis can coexist. The question of operation or no operation will then have to be decided upon the merits of the individual case.

So far as our knowledge goes, writers generally speak of pain as one of the symptoms of pericarditis. This pain may be conducted to the epigastrium. McFederan[1] speaks of severe epigastric pain with immobility of the diaphragm and nausea and vomiting.

Fussell[2] speaks of the pain present in pericarditis being sometimes referred to the appendicular region and also calls attention to the occasional difficulty of differentiating appendicitis and pericarditis. He[3] calls attention to the necessity of differentiating appendicitis from pericarditis.

Wynter[4] says that in a majority of the cases affecting the lung

[1] Osler and McCrae: Modern Medicine.
[2] Pericarditis, Tyson's Practice of Medicine.
[3] Monographic Medicine, 5.
[4] Absence of Abdominal Respiratory Movements as an Indication of Pericarditis, Clinical Journal of London, 1913.

and the pleura the abdominal breathing is one-sided, whereas the influence on abdominal movement in pericarditis is bilateral, and hence absence of abdominal movement in pericarditis is as obvious as in abdominal conditions, though rigidity and tenderness are for the most part lacking in pericarditis.

He reports two cases in which remarkable stillness of the abdomen led to the diagnosis of perforated gastric ulcer in one case and of appendicitis in the other. The case of supposed appendicitis was operated upon and a normal appendix was removed without adhesions.

He concludes that in a case in which the loss of abdominal movement is marked in the absence of an obvious lung or abdominal lesion, pericarditis should be considered.

The explanation given by Mackenzie[5] for the transference of pain in visceral diseases is as follows:

1. Stimuli which produce pain in the external body wall are not adequate to produce this sensation when applied to the viscera

2. Violent contraction of a non-striped muscle fiber produces pain, but that the region in which the pain is felt is different from that in which the contracting muscle lies, and that when a sensory muscle is stimulated in any part of its course in the brain, the cord, or the trunk of the nerve the pain is distributed to the peripheral distribution of the nerve in the external body wall. This is his so-called viscerosensory reflex.

He further considers that in order to call into effect this viscerosensory reflex there must be an adequate stimulus, and one may consider that because the stimulus is rarely adequate in pericarditis, pain in this condition is not always transferred either to the arm, the epigastrium (which is the most common seat of referred pain) or to the lower abdominal wall, which is the rarest seat of localization of the pain.

His visceromotor reflex may explain the rigidity of the abdominal wall in these cases.

PERICARDITIS IN CHRONIC NEPHRITIS.*

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Although the occurrence of acute pericarditis in advanced renal disease has long been known the mechanism of its origin is still obscure. Interest in the subject was aroused by a recent case. The patient was a girl, aged nineteen years, suffering from an end-stage chronic nephritis. After the development of a severe acidosis

[5] Diseases of the Heart.

* From the Medical Clinic of the Presbyterian Hospital, New York.

and a fibrinous pericarditis she finally succumbed. When at the suggestion of Dr. Longcope other cases of acute pericarditis in nephritis were reviewed it was found they fell into a recognizable group having fairly well-defined clinical and laboratory characteristics. The pathogenesis of the pericarditis was further studied by correlating the bacteriological with the pathological findings. The facts brought out were thought to throw an additional light upon the etiology of the complication.

In the cases of renal disease originally described by Bright[1] (1836) acute pericarditis is listed in 8 out of 100 autopsies. He regarded it as part of a general tendency toward involvement of the serous membranes. In the same series the pleura was acutely involved in 16 cases and the peritoneum in 12. Special emphasis upon the frequency of pericarditis in chronic nephritis was given by Taylor[2] (1845), who described it in 5 out of 51 cases that he examined post mortem. It is interesting to note in passing that five years later Taylor concluded that whereas practically all the cases of rheumatic pericarditis got well those following renal disease were uniformly fatal. Von Bamberger[3] states, according to his own observations, that 14 per cent of cases of Bright's disease develop pericarditis. The incidence given by other writers varies. Rosenstein[4] 7 per cent, Frerich[5] 4.5 per cent, M. Rayer[6] 5.4 per cent. Sibson[7] made an exhaustive study of the subject and in 1691 collected cases of nephritis found the incidence 8.1 per cent. In his personal series of 285 cases there were 25 cases of acute pericarditis, or 8.8 per cent. Sibson mentions 2 cases of this latter group occurring in acute nephritis and the remainder in chronic nephritis.

In the autopsy group here presented of 162 cases of nephritis 18 had acute pericarditis, or 11.1 per cent. In a clinical group represented by cases of nephritis admitted to the hospital during the corresponding period, out of 929 cases there were 30 who developed pericarditis, or 3.2 per cent. The latter figure may be said to express the incidence of the complication in non-fatal and fatal nephritis, the autopsy statistics naturally representing the incidence in fatal cases alone. Approached from the viewpoint of the causes of pericarditis in general, Sears[8] found chronic nephritis operating as a factor in 7 out of 100 cases, or 7 per cent; Preble,[9] analyzing 300 cases in 11.2 per cent. Locke[10] studied pericarditis as it occurred in 3683 routine autopsies; 4 per cent of all autopsies showed an acute pericarditis. Evidence of this complication in the clinical notes was present in 17 per cent. In 150 autopsies of acute pericarditis 16 were associated with nephritis, or 11 per cent. Of these 8 were grouped as fibrinous pericarditis, 6 adhesive (total or partial) and 2 purulent. Hirschfelder[11] states that pericarditis occurred in 230 (1 per cent) of the cases admitted to the medical service of the Johns Hopkins Hospital. Of these 33 were associated with nephritis, or 14.3 per cent. According to the statistics of these authors,

nephritis comes third as a cause of pericarditis, pneumonia and rheumatism only being more frequent. Sinnhuber[12] places rheumatism first, nephritis second, and the pyogenic infections afterward.

Concerning the pathogenesis of this complication in nephritis standard text-books are either non-committal or at variance with each other. Whether the cause lies in chemical irritation or secondary infection remains undetermined, as expressed by Gibson.[13] Aschoff[14] makes a similar statement. MacCallum,[15] speaking of the frequent occurrence of pericarditis in nephritis, says, "In these cases it is generally difficult to find any bacteria." Hirschfelder[16] states that "it is usually due to an intercurrent infection, and the pyogenic cocci can often be cultivated from the exudate." According to Wells[17] "the uremic pericarditis and endocarditis, which have often failed by ordinary methods to yield any bacteria, are apparently toxic processes." Sinnhuber[12] (1911) says that since neither cultures nor microscopic researches have shown bacteria it is apparently a toxic inflammation.

The clinical group comprises 30 cases. As all the factors studied were not present in every case the proportion of each will be mentioned. The laboratory data collected were selected at or near the onset of the pericarditis in order that they should represent factors which perhaps predisposed toward the complication. They are not then the most extreme findings, and are not at all in most instances antemortem statistics. This will be seen more clearly when the duration of life, after development of the pericarditis, is discussed.

The patients were mostly just below middle age, the average age being thirty-seven years, the extremes fifteen years and fifty-seven years. There were an equal number of males and females. All were diagnosed chronic nephritis. No case of acute nephritis developed the complication, nor was there a case of pure salt-and-water retention nephritis (nephrosis). The cardinal features included a uniformly marked elevation in blood-pressure; a severe secondary anemia; moderate leukocytosis and polynucleosis; a distinct hemorrhagic tendency; a greatly increased blood-urea nitrogen; minimal phenolsulphonephthalein excretion and a conspicuous acidosis.*

* Acidosis is used her to mean a lowering of the bicarbonate reserve of the blood and does not necessarily indicate any change in the H-ion concentration. In these cases the diminution in available alkali no doubt arose through an increase in non-volatile acid. It is, of course, impossible to say by a determination of the plasma CO_2 whether the H-ion concentration of the blood persisted normal or underwent an actual shift in the acid direction, i. e., whether the acidosis was compensated or uncompensated. (Terms originally used by Hasselbach, K.A., and Gammeltoft, S.A., Biochem. z. 1915, **68,** 205, and adopted by Van Slyke, Donald D., and Cullen, Glenn E., Jour. Biol. Chem., 1917, **21,** 293). This important point can in the future be satisfactorily determined by constructing the so-called carbon dioxide diagram of the blood. (Haggard and Y. Henderson (Jour. Biol. Chem., 1919, **39,** 163). It has recently been applied to a series of hospital patients by Means, Bock and Woodwell (Jour. Exp Med., 1921, **32,** 201), and its value in determining actual changes in blood reaction has been demonstrated.

The average blood-pressure of the 30 cases was 214/136, the lowest 170/110. The average red blood cell count of 22 tested cases was 2,738,000, the hemoglobin 48 per cent. In no case was there absence of anemia. The majority of the cases showed a moderate leukocytosis, with polynuclear predominance at the time of development of the pericarditis. The average of 29 cases was 15,900 for the white count, polynuclears 87 per cent; 2 cases only showed a white blood count under 10,000. The temperature was variable, often showing a slight elevation, rarely more than 1° or 2°. A distinct tendency to hemorrhage was noted in 21 of the 30 cases, or 70 per cent. This varied in degree and was manifested in various ways, commonly as petechiæ, purpura of the skin or mucous membrane, epistaxis, hematemesis and rectal hemorrhages.

The average blood urea of 28 cases was 2.69 gm. per L. All were considerably elevated except one case, (No. 29), which had 0.45gm per L. This patient had general arteriosclerosis with a blood-pressure of 300/200, albumin and casts in the urine without fixation of the specific gravity, and, in addition, aortic valvular heart disease. The pericardial friction lasted four days and the patient improved and left the hospital. He died one and a half months later at home. The nephropathy here would perhaps be grouped as an arteriosclerotic kidney. Elevation of the blood urea in cases of nephritis with acute pericarditis has been commented upon by French authors (in the French, "pericardite brightique"). In a series of 11 cases of Widal and Weil[18] the average was 2.71 gm. per L. Chalier and Novi-Jusserand[19] report 1 case in full in which the blood urea was 2.10 gm. per L. Other individual cases are mentioned by d'Ulrici,[20] 4.85 gm. per L., Froment and Rochaix,[21] 3.57 gm. per L., and Foy[22] 2.54 gm. per L. In comparing the average of this series, 2.69 gm. per L., it must be remembered that this value does not represent the maximal values of the cases, but the finding on or near the day when the pericardial rub first became evident. As will be emphasized later the blood urea progressively mounted. (See Table I for clinical data.)

In all of the 16 cases in which observations were made an acidosis, as evinced by a lowering of the plasma bicarbonate, was present. In 9 cases the figures were obtained by the carbon dioxide combining power of the plasma by the method of Van Slyke,[23] and averaged 28.7 vol. per cent. In 7 earlier cases the results are recorded by the carbon-dioxide tension of the alveolar air (Fridericia method), and averaged 24.59 mm. Hg. The lowest observation was 11.8 vol. per cent, plasma CO_2. (Some of the cases at times showed lower figures than are listed in the table, but here too those were selected which had the nearest time relationship to the onset of the pericardial friction.) A conspicuous diminution of the available blood alkali is thus evident from both methods. That most patients with advanced nephritis, especially in the last stages of

TABLE I.—CLINICAL DATA.

Case.		Age.	Sex.	B. P.	W. B. C.	Diff. polys., per cent.	R. B. C.	Hgb., per cent.	Bl. urea gms. per L.	Bl. CO_2	Phthalein per cent.
1	E. P.	48	F	214/105	19,000	88	2,200,000	60	3.92	31.2 vol. per cent	
2	W. D.	50	M	210/150	13,000	88	1,000,000	15	2.50	26.6 mm. Hg.	8.0
3	J. G.	36	M	224/130	24,000	92	3,000,000	47	2.50	19.7 "	0
4	C. L.	49	F	200/140	18,200	92	3,200,000	64	3.73	.....	0
5	D. V.	44	M	208/126	16,000	..	3,000,000	50	2.70	19.2 "	0
6	W. F.	26	M	226/140	19,000	86	2,620,000	52	2.91	.....	0
7	C. A.	29	F	215/145	29,000	89	3,350,000	50	3.07		
8	M. E.	40	F	214/136	.....	..	.....	..	1.50		
9	T. L.	44	M	222/150	15,200	88	3,736,000	70	3.87	38.5 vol.	0
10	C. K.	15	M	200/130	23,700	80	2,912,000	40	4.45	22.1 "	0
11	A. K.	40	F	205/130	6,000	75	3,480,000	70	3.11	24.0 "	0
12	W. S.	37	M	170/135	14,000	80	4,000,000	55	1.58	47.0 "	15
13	E. S.	21	F	170/110	11,200	89	1,700,000	20	4.98	32.8 "	
14	T. S.	50	M	220/122	13,000	80	3,500,000	50	4.12	21.4 "	1
15	L. M.	19	F	180/110	10,200	68	1,300,000	30	2.95	11.8 "	
16	T. S.	48	M	218/110	23,800	91	3,400,000	55	1.85	25.2 mm. Hg.	7
17	H. W.	19	F	178/110	11,500	88	1,475,000	32	2.50	22.75 "	
18	A. W.	40	F	244/152	13,800	84	.....	..	2.61		
19	R. A.	48	M	210/148	12,000	67	.....	..	1.77		
20	M. G.	36	F	220/180	9,400	82	.....	50	3.72	.....	34
21	L. L.	38	M	210/138	14,100	72	.....	70	2.20	.....	0
22	H. P.	44	M	210/140	20,000	83	.....	..	.....	.....	10
23	L. J.	36	F	176/90	8,460	74	1,480,000	30	.....	.....	10
24	R. T.	35	F	195/100	17,000	90	1,828,000	38	2.44	.....	3
25	E. S.	32	F	255/175	19,800	92	2,380,000	45	3.14	30.5 vol. per cent	0
26	B. G.	37	M	230/150	15,150	89	4,600,000	69	1.60		
27	E. H.	46	F	250/140	14,500	74	3,500,000	46	1.75		
28	J. E.	57	M	212/140	17,200	90	.....	..	1.14	.....	6
29	L. H.	42	F	300/200	15,000	76	.....	..	0.45	29.45 mm. Hg.	9
30	V. F.	29	M	228/162	19,000	95	2,584,000	42	2.27	.....	15
Average		37.8	M50%	214/136	15,936	87	2,738,409	48	2.69	29.25 "	
										28.7 vol per cent	5.9
										24.59 mm. Hg.	

the disease, have a demonstrable acidosis has been shown by Henderson and Palmer,[24] Peabody,[25] Chace and Myers[26] and others. According to the figures of this series 100 per cent of the tested cases had an acidosis at the time of onset of the pericarditis, in most instances of severe grade, represented as it was by an average plasma CO_2 of 28.7 vol. per cent.

The average phenolsulphonepthalein excretion in 20 cases was 5.9 per cent; in one-half of these it was zero. No proportional relationship could be established between the degree of acidosis, the elevation in blood urea or the excretion of phthalein. This is in accordance with the similar earlier observation of Peabody.[25]

In 26 of the 30 cases a pericardial friction-rub was described in the clinical notes. In 1 additional case the diagnosis was made by signs of effusion. The diagnosis was thus made clinically in 90 per cent of the cases. The frequency with which the diagnosis was made by a friction-rub may perhaps be accounted for by the small amount of pericardial fluid that is present in this type of pericarditis (as will be seen later). The average duration of the rub was eight days;* in one case it could be heard for two and a half months. The average length of life after the appearance of the rub was twenty-nine days. One patient, in whom the pericardial friction lasted nine days, lived for one year thereafter. If this case were not included the average length of life after the rub became evident would be sixteen days. Another patient lived two months after the onset of the pericarditis; a third two and a half months, and a fourth four months. This is mentioned to emphasize that the pericarditis is not always a terminal complication. It may subside and the patient undergo a remission of symptoms, leave the hospital and perhaps live comfortably for several months. The case mentioned above that lived for one year showed at autopsy an adherent pericardium.

The pericarditis does not seem to be the direct cause of death in many of these cases. In some of them it seems related rather to the increasing retention of nitrogen in the blood. The acidosis too does not appear responsible for the final succumbing of the patient. In these cases it was generally combated with sodium bicarbonate whenever it became dangerously low. The case of L.M. may be taken as an example: At the time of her admission to the hospital, when the pericarditis was first noted, the blood urea was 2.95 gm. per L. and the plasma CO_2 11.8 vol. per cent. The friction-rub persisted until death, sixteen days later. Bicarbonate was persistently administered, aiming to keep the blood CO_2 at least above

* It must be remembered that the duration of the rub applies to hospital residence. In some cases the rub was present on admission and an accurate estimation of its actual duration is thus not possible.

40 vol. per cent. The determinations ran as follows: 11.8 vol. per cent, 10.9 vol. per cent, 27.1 vol. per cent, 48.1 vol. per cent, 40.4 vol. per cent, 46 vol. per cent. At the same time the blood urea mounted 2.95 gm. per L., 3.17 gm. per L., 3.55 gm. per L., 4.75 gm. per L. The cause of death did not seem linked with progressive heart failure nor obviously with the acidosis, but rather with the progressive retention of nitrogen in the blood.

Of the 30 cases 18 came to autopsy. The kidney lesion was predominantly the contracted granular kidney, more commonly the glomerular than the arteriosclerotic contracted kidney. Sibson's[7] cases occurred very largely in the small granular kidney. Lecorche and Talamon[27] also believed pericarditis to be more frequent in this interstitial form of the disease. According to Grainger Stewart[28] however, it was equally common in the parenchymatous and renal cirrhosis. No attempt has been made in this series to correlate the anatomical lesions with the clinical grouping of the nephritis.

The pathology of the pericarditis possesses special interest because of its relation to some of the bacteriological findings. The pericardial cavity contained in most instances a little increase in fluid, 12 of the 18 cases having between 50 and 200 cc; 2 showed no fluid; 1 had an adherent pericardium; 3 had a large excess of fluid; in 1, 700 cc of bloody fluid; another that had been tapped during life contained 2000 cc of dark red fluid in the pericardial cavity. Chalier and Novi-Jusserand's[29] case had 250 gm. and Widal and Weil's[30] cases between 50 and 250 gm. of pericardial fluid. The fluid was usually of a light or dark amber color, clear or only slightly turbid. Fibrinous adhesions were almost always present, appearing either as thin delicate bands or as a fine fibrinous deposit. Microscopically the fibrin network was free from cells beyond occasional scattered round cells. The epicardium, as a rule, was a little thickened and in the majority of cases contained a slight to a moderate infiltration of small mononuclear cells—in a few instances no infiltration at all. In 2 cases the mononuclear infiltration extended into the muscle substance. In 5 cases, however, a polynuclear infiltration was present, with smaller numbers of mononuclear cells as well. In 4 of these the polynuclear infiltration was present in the pericardium. In 1 case the pericardium was infiltrated moderately with mononuclear cells, but the smear of the pericardial exudate showed pus, blood cells and bacteria. Of the 5 cases showing polynuclear infiltration 4 were cultured, and all of these showed the presence of pyogenic organisms. The fifth had a sterile blood culture, but no culture had been made from the pericardium. In 2 of the cases the organisms were recovered in pure culture, one a hemolytic Staphylococcus aureus and the other a short-chain streptococcus. The third showed Staphylococcus albus and B. coli communis; the fourth, a non-hemolytic streptococcus, a bacillus belonging to the

Friedländer group and a Gram-negative bacillus which did not form gas with dextrose. In 2 of the cases in which a blood culture was done at the same time the same organisms were recovered, indicating there was a terminal septicemia, the pericardium constituting a localization of the infectious process. In the remaining 12 cases in which polynuclear infiltration was not demonstrated there were 4 cases that were tested bacteriologically and the pericardium found free from infection in all. There was 1 of these cases that had a terminal bronchopneumonia in which the lung culture at autopsy yielded a pneumococcus IV, but in which the pericardium was sterile both in aërobic and anaërobic culture. (See Table II for bacteriological and pathological data.)

It is interesting even in this small group that the 4 cases with frank infection showed a polynuclear response in the epicardium or in the pericardial exudate, whereas the 4 cases in which no infection of the pericardium was present showed an absence of polynuclear leukocytes, and, instead, mononuclear infiltration or no cellular infiltration whatsoever. Of the 4 sterile cases, in 3 the cellular response in the pericardium varied from just a few scattered mononuclear cells to a moderate infiltration. In the fourth only the pericardial fluid and fibrin tags were available, and these showed no cells at all. This division of cases brings forth the obvious suggestion that there may actually be two distinct etiologies for the complication, an infectious and a non-infectious. Before this is further discussed the bacteriological findings in the literature as well as the experimental evidence will be reviewed. This has been delayed up to this point in order that the histology of the pericarditis might be compared with the bacteriological findings on the basis of the above results. No purposeful comparison has previously been made, nor do many of the reports contain the material for doing so.

The review of all authentic reports concerning the bacteriology of pericarditis in nephritis shows 33 in which the bacteriology of the pericardium was investigated (31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42). Except for the more recent article by Widal and Weil most of the studies were made before many of the more recent methods of bacteriological research were instituted, and therefore have only a limited value. Of these cases, however, 18 were sterile and 15 showed bacteria, usually of the pyogenic variety. The most frequent invader was the pneumococcus and the next frequently found was the Bacillus coli and the streptococcus. The attempt to link up the histology of the pericardium with the bacteriological findings in the cases previously reported yields a partial confirmation of the results in our series. When infection was present polynuclear leukocytes were described in the pericardium or pericardial exudate in each instance in which individual case reports were given.

TABLE II.—PATHOLOGICAL AND BACTERIOLOGICAL DATA.

Case.	Duration of rub, days.	Length of life after onset of pericarditis days.	Chest involvement.	Tendency to hemorrhage.	Pathology of pericardium.	Bacteriology.
1 E. P.	1	3	None	Moderate hematemesis blood in stool.	Autopsy by Dr. Lamb, 100 cc pericardial fluid, amber, and slightly turbid. Strands of fibrin cover pericardial surfaces. Petechial hemorrhages on visceral pericardium. Microscopical lymphocytes, poly infiltration and edema.	Smears from pericardial fluid at autopsy showed a non-hymolytic streptococcus, a bacillus belonging to the Friedländer group, and a gram negative bacillus which does not form gas with dextrose. (Air was found in blood vessels in this case.)
2 W. D.	3	3	Pleurisy	Marked; rectal hemorrhage; brain hemorrhage; skin petechiæ.	Autopsy by Dr. Evans. Large excess of cloudy yellow fluid. Fine diffuse fibrinous deposit. Microscopical fibrin is scanty and contains a few round cells.	No cultures of pericardium.
3 J. G.	4	4	Hydrothorax	Marked; rectal hemorrhage. Epistaxis	No autopsy.	Two blood cultures during life sterile. No cultures of pericardium.
4 C. L.	4	4	None.	Moderate; hemorrhage in intestines and stomach; petechiæ on skin.	Autopsy by Dr. Meierhof. Fine fibrinous exudate over part of pericardium. Microscopical a very few cells are seen, of small mononuclear type.	No cultures of pericardium.
5 D. V.	8	8	Pleurisy.	Moderate; rectal hemorrhage; petechia on skin.	Autopsy by Dr. Mueller. Fresh fibrinous exudate. About 200 cc pericardial fluid. Abundant infiltration of small and large mononuclear cells, which extend into muscle. Few scattered polys.	No cultures of pericardium.
6 W. F.	(1)	..	Pleurisy.	Moderate; bleeding gums; epistaxis.	Autopsy by Dr. Mackenzie. 150 to 200 cc rather dark, slightly turbid, amber fluid. Fresh granular fibrin. Microscopical numerous small mononuclear cells. Occasional poly.	No cultures of pericardium.
7 C. A.	1	1	Hydrothorax.	Very slight.	No autopsy.	

[1] Diagnosis not made clinically.

8	M. E.	3	3	None.	None.	No autopsy.	Blood culture showed pneumococcus II. Pleural fluid also pneumococcus II. No cultures of pericardium.
9	T. L.	4	8	None.	Marked; rectal hemorrhage; hematuria; epistaxis.	Autopsy by Dr. Stier. No fluid. Fine fibrinous adhesions. Muscle shows scattered areas of whitish color and smaller areas of darker red color, apparently hemorrhages. Microscopical fibrinous adhesions contain very few cells. Beneath them are numerous small mononuclear cells, with an occasional poly.	By Miss Cooper. Lung culture at autopsy sterile. No pericardial culture.
10	C. K.	13	13	Pleurisy.	Marked; epistaxis; hemorrhage from bladder and into skin.	Autopsy by Dr. Eggstein. Increased pericardial fluid. Firm white fibrinous masses in some places in others delicate fibrinous exudate. Microscopical loose fibrinous network, with only an occasional scattered small mononuclear.	No cultures.
11	A. K.	1	1	Hydrothorax.	Slight; bleeding gums.	No autopsy.	No cultures.
12	W. S.	9	1 yr.[2]	Pleurisy.	None.	Autopsy by Dr. Eggstein. Pericardium is adherent, and shows considerable mononuclear infiltration.	No cultures.
13	E. S.	5	5	None.	Very marked; bleeding from gums, stomach, rectum, and vagina; epistaxis.	No autopsy.	No cultures.
14	T. S.	3	5	None.	None.	No autopsy.	No cultures.
15	L. M.	16	16	None.	Marked; hematemesis; epistaxis.	Pericardial puncture. Clear amber fluid with fibrin shreds. No cells in smear; no autopsy.	Pericardial fluid aspirated three hours after death sterile.
16	T. S.	([3])	..	Hydrothorax.	None.	Autopsy by Dr. Meierhof. 100 cc of yellow turbid fluid. Fresh fibrinous adhesions between parietal and visceral pericardium. Microscopical fibrin tags are without cellular infiltration. Lymphocytes present beneath epicardium.	By Miss Frazier. Culture of lung at autopsy showed a pneumococcus II. Culture of pericardium was sterile, aërobically and anaërobically.

[2] Died one year later. Autopsy showed an adherent pericardium.

[3] Diagnosis not made clinically.

TABLE II.—PATHOLOGICAL AND BACTERIOLOGICAL DATA.—(*Continued*)

Case.	Duration of rub, days.	Length of life after onset of pericarditis days.	Chest involvement.	Tendency to hemorrhage.	Pathology of pericardium.	Bacteriology.
17 H. W.	(1)	14	Pleurisy hydrothorax.	Moderate; epistaxis.	Autopsy by Dr. Evans. Pericardial fluid, dark red, 2000 cc. Fine fibrinous deposit. Petechial hemorrhages over the pericardium. Microscopical small round cells present beneath the fibrin. (Tapped during life.)	By Miss Olmstead. Blood culture during life sterile. Blood culture at autopsy sterile. Smear or pericardial fluid obtained by tapping during life showed no organisms.
18 A. W.	7	7	None.	Moderate; petechiæ; hemorrhages in conjunctiva; blood in colon irrigation.	Autopsy by Dr. Eggstein. Pericardium covered by many shaggy irregular fibrinous adhesions. These are bright red with a few areas of grayish mottling suggesting pus. In places fibrin 1 cm. thick. Microscopical exudate consists of polys, fibrin, red cells and masses of bacteria.	Autopsy culture of spleen and liver showed hemolytic staphylococcus aureus. Smear of heart showed many Gram-positive cocci, probably staphylococci.
19 R. A.	1	1	Pleurisy	None.	Autopsy by Dr. Mueller. Light fresh fibrinous exudate. Slight increase in fluid which is rather turbid. Fibrous layer of epicardium the seat of a moderate infiltration of polynuclear leukocytes and a few round cells.	By Miss Olmstead. Pericardial culture showed B. coli communis and staphylococcus albus. Gram-negative bacilli and Gram-positive coccus were seen on the smear.
20 M. G.	3	3	None.	Moderate; epistaxis; splitting up of blood.	Autopsy by Dr. Evans. Fine fibrinous exudate. No fluid. Epicardium distorted. It is edematous, infiltrated with plasma cells, polys, small round cells; and shows a fibrinous deposit.	By Miss Olmstead. Blood culture at autopsy sterile. No culture of pericardium.
21 L. L.	8	8	Pleurisy; hydrothorax.	Shown at autopsy; hemorrhages in brain, stomach and bladder.	Autopsy by Dr. Stillman. Brown turbid fluid, not in excess. Many flakes of fibrin over a dull pericardium. No cellular infiltration.	No pericardial culture.

(1) Diagnosed by signs of effusion, fourteen days before death.

22	H. P.	4	4	Pleurisy.	None.	Autopsy by Dr. Pappenheimer. 100 cc pale yellow fluid. Large flakes and shreds of fibrin. Fresh adhesions; microscopical epicardium not seen.	No pericardial culture.
23	L. J.	80	80	Pleurisy.	Moderate; epistaxis; coughed up blood.	Autopsy by Dr. MacCallum. 700 cc bloody fluid. Thickened pericardium. Soft fresh fibrinous exudate. Pericardium is infiltrated moderately with mononuclear wandering cells and infrequent polys. Fibrin almost free from cells. Smear of pericardial fluid: pus, blood cells and Gram-positive cocci.	By Dr. Soper. Smear of pericardial fluid showed pus, blood-cells, and Gram-positive short-chained cocci. Culture was pure streptococcus.
24	R. T.	8[5]	29	No autopsy; pleurisy.	Moderate; hematemesis; epistaxis.	No autopsy.	No culture of pericardium.
25	E. S.	2	2	None.	None.	No autopsy.	No culture of pericardium.
26	B. G.	3	3	None.	None.	No autopsy.	No culture of pericardium.
27	E. H.	([6])	..	Pleurisy; hydrothorax.	Slight; vomited clots of blood.	Autopsy by Dr. Evans. No excess of fluid. Delicate fibrinous deposit. Small mononuclears in epicardium.	No pericardial culture.
28	J. E.	20	120[7]	Hydrothorax.	Slight; rectal hemorrhage.	No autopsy. (Patient went home improved. Died three months later.)	No pericardial culture.
29	L. H.	4	60	None.	None.	No autopsy.	No pericardial culture.
30	V. F.	2	2	None.	Marked; purpura of skin and mucus membranes; bloody urine.	Autopsy by Dr. Allison. Thin fibrinous adhesions; 50 to 100 cc clear fluid. Leukocytic infiltration, mostly mononuclears, extending a short way into muscle.	By Miss Olmstead. Pericardial culture sterile.
Average		8	29	56.6 per cent.			

[5] Rub lasted eight days. Patient then left the hospital. Died three weeks later.

[6] Diagnosis not made clinically.

[7] Rub lasted twenty days and then disappeared. Patient left the hospital improved. Died three months after departure, four months after disappearance of rub.

The experimental production of acute pericarditis in animals by simulating the kidney damage in man has been productive largely of negative results. The ligature of both ureters or double nephrectomy is not followed by pericardial inflammation (Banti,[43] Keraval,[44] Beco,[45] Chatin and Guinard[46]). (One out of the five rabbits in Beco's series developed an acute serofibrinous pericarditis following ureter ligature. The pericardial fluid was sterile, but Beco admits the case is a bizarre one and does not prove the chemical theory.) Banti[47] also performed these experiments by first producing a point of lowered resistance through cauterization of the pericardial surface. An acute pericarditis develops which is more marked and of quicker onset than the control pericarditis that follows cauterization alone. This evidence, however, can hardly be accepted as proving anything definite. Keraval[48] injected urea and ammonium carbonate into the pericardial cavity without causing pericarditis. Chatin[49] found the serum of cases of "pericardite brightique" hypotoxic to animals rather than hypertoxic. These authors, because of the negative clinical bacteriology, nevertheless believed chemical irritation to be the main cause of pericarditis in chronic renal disease.

The observation of Flexner[50] upon terminal infections occurring in chronic diseases such as cirrhosis of the liver, diabetes mellitus and chronic nephritis shows that a local or general invasion by bacteria is frequently the immediate cause of death. Pericarditis, however, is especially characteristic as a complication of nephritis and not of other chronic affections. Although it may occur occasionally as a terminal infection in any chronic disease, there is an additional frequency in renal disease unexplained by the factors of infection.

Further evidence upon the etiology of this complication is of indirect nature. To determine whether the pericarditis had any relation to involvement of the other serous membranes, the incidence of involvement of the pleural cavity was tabulated in the cases that had pericarditis. Fibrinous pleurisy was present in 25 per cent, fibrinous pleurisy or hydrothorax in 56.6 per cent, peritonitis in none.

In the interest of the chemical theory an analogy may be drawn from the reactive pericarditis that follows infarction of heart muscle as after coronary closure. Here presumably a sterile chemical irritant derived from the products of muscle necrosis produces the pericarditis. Fischer[51] (1897) in fact explained the nephritic pericarditis upon very similar reasoning. He proposed that a myocarditis existed in uremia and that the irritant effect of the damaged muscle cells caused an inflammation in the adjoining serous layer of the pericardium. Rhomberg[52] has found in simple endocarditis thrombosis of the myocardial vessels and myocardial degeneration. Stengel[53] would couple this with what occurs in pericarditis, believing

that the symptoms of the latter are due to the underlying myocardial disease. Changes in the muscle fibers were observed in many of the cases of this series and occasionally mononuclear leukocytes were seen to invade the muscle nearby; but there was not enough of constancy either in location or character of the pathology to warrant any conclusions being drawn.

Comment. There are, then, two distinct theories that have been advanced to explain the etiology of this complication: (1) bacterial and (2) chemical. On the basis of the bacterial origin it may be stated that in a small group of cases microörganisms have been cultured from the inflamed pericardium. These organisms are of the same nature as those found by Flexner in the general and local infections of chronic renal disease. Furthermore the characteristic response to infection is shown by the presence of polynuclear leukocytes in the pericardium or pericardial fluid. This histology of the infected cases is demonstrated in the present series and in the infected cases reviewed in the literature. The evidence seems definite that in a small proportion of cases infection is the cause of the pericarditis.

In support of the chemical origin of the complication, the greatest argument is perhaps the existence of cases that have been found sterile after careful culture. Not only have aërobic and anaërobic cultures been made on very diverse media, but the pericardial fluid has been injected into animals, subcutaneously and intraperitoneally, with negative results. An additional important consideration is the non-infectious nature of the toxemia. The presence of a marked elevation in blood urea has been commented upon by French observers. Our results confirm the nitrogen retention and show in addition that there is simultaneously a notable acidosis and that both findings are present at the onset of the pericarditis. The secondary anemia was constantly present and generally severe. The tendency to hemorrhage was a conspicuous feature. As further evidence the differing pathological histology of the sterile group may be stressed. The pericardium of the sterile cases showed no infiltration with polynuclear leukocytes, but instead the presence of mononuclear leukocytes, or, infrequently, no cellular infiltration whatever. The remainder of the cases not cultured showed the pathological characteristics of the sterile group. This histology of the sterile group finds partial confirmation in the literature. In Chatin's carefully described case, mononuclear infiltration in the pericardium is fully noted; not so the cases from Banti's clinic, in which, however, the histology is incompletely given. The presence of round cells in an inflammatory area brings forth the possibility of a tuberculous etiology. Tuberculosis of the pericardium is not uncommon. However, this was not the pathology here. The mononuclear leukocytes were more likely to be scattered than localized; there were no tubercles, giant cells or characteristic granulation

tissue. The suggestion of a chemical irritant as cause of the majority of the cases is thus entirely compatible with the chemical nature of the toxemia and with the bacteriology and pathology of the condition. A clear-cut example of a pericarditis of non-infectious and therefore chemical origin is found in the acute pericarditis that follows infarction of heart muscle.

The possibility that both factors may have been present in an individual case presents itself. A pericardium previously inflamed, in response to a chemical agency, may finally become the seat of a terminal infection. For this reason sharp division of the cases may not always be possible. Case No. 23 may be mentioned as perhaps an example and the facts briefly outlined. In this case the pericardium showed a mononuclear infiltration, whereas the pericardial fluid contained pus and numerous cocci. The culture gave a pure streptococcus representing apparently a terminal infection. And yet the patient had had pericarditis for two and a half months before death. None of the other infected cases lived longer than seven days and the average was less than four days. Of the proved sterile cases, three were diagnosed and the average length of life after the onset of pericarditis was over ten days. The remainder of the cases fell pathologically into the sterile group and gave a considerably longer duration of life. The paucity of the proved cases and the complexity of the other findings limit the value of further comparisons.

Summary. 1. A description is given of the clinical and laboratory characteristics of a group of 30 cases of chronic nephritis at the time of development of an acute pericarditis. A marked nitrogen retention in the blood, a constantly present acidosis, a high blood-pressure, severe secondary anemia and a tendency to hemorrhage were conspicuous features.

2. It is pointed out that pericarditis is not a terminal complication in the sense that it always terminates the life of the patient. The average duration of life after the onset of the pericarditis was twenty-nine days. Excluding a patient that lived one year thereafter the average figure was sixteen days.

3. Death in many of these cases did not seem linked with an advancing heart failure or to the acidosis, but rather to the progressive retention of nitrogen in the blood.

4. Except in one case the diagnosis was made by the presence of pericardial friction and not by the signs of effusion. The diagnosis was made clinically in 90 per cent of the cases.

5. In 4 cases direct culture of the pericardium yielded pyogenic organisms. In 4 other cases culture of the pericardium was sterile. In the infected cases the cellular infiltration of the pericardium was predominantly of the polynuclear type; in the sterile cases the infiltration was predominantly of mononuclear type. The cases in which the pericardium was not cultured showed the pathological characteristics of the sterile group.

6. Reasons are given for believing that the majority of cases of pericarditis in chronic nephritis are of non-infectious origin. The assumption of a chemical irritant as cause of the complication is entirely compatible with the chemical toxemia of the patient and with the bacteriological and pathological findings in the pericardium.

7. A small group of cases exists in which frank infection of the pericardium is present. It is believed that the pericarditis in this group is generally of true infectious etiology. The possibility is present, however, that the complication may sometimes be of chemical origin and the inflamed pericardium become secondarily infected.

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BILIARY TRACT DISEASE: SOME LESSONS LEARNED FROM DUODENOBILIARY DRAINAGE. FUTURE PROBLEMS. CITATION OF CASES.*

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Four years have now elapsed since the late Professor Samuel J. Meltzer announced the effect that magnesium sulphate produced on the duodenum and on Oddi's sphincter of the common duct when locally introduced,[1] and four years have likewise elapsed since this

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observation of Meltzer's was applied clinically by means of the duodenal tube in the diagnosis, and, later, in the treatment of diseases of the biliary tract. Around this has gradually been built up a method of non-surgical drainage of the duodenobiliary tract which has already been proved to have great merit in diagnosis and is being proved to have a great field of usefulness in treatment. Much of the evolution of the technical details of this method have been published in earlier papers [3, 4, 5, 6, 8, 12]. A certain period of time must elapse before an estimate of this *method of treatment* can be properly made. During the past year a number of articles have been published which indicate that there is a general and widespread interest in this work. Brown[9] has favorably reported his results in a series of some 70 cases, the method being used principally for diagnosis. Einhorn[13] in a paper dealing with the action of various salts when introduced into the duodenum has attempted to put forward another explanation for the color changes following the installation of magnesium sulphate. In this article he has carefully noted the changes in the physical and clinical properties of the bile obtained, but we believe he has entirely misinterpreted their meaning. If Dr. Einhorn will follow our technic in detail or improve his own we feel convinced that as his personal experience with this method enlarges he will satisfy himself that our original premises are correct. Smithies[14] in a very complete paper has presented his favorable attitude toward the usefulness of this method of non-surgical drainage as an aid to both diagnosis and treatment. Recently, Whipple[15] has written on it from the surgical viewpoint and has emphasized its value as an aid to preoperative diagnosis. Also reference to this method can be found in chapters by Sir Humphrey Rolleston on gall-tract diseases which appear in the *Oxford Loose-leaf System of Medicine*.

Still more recently Simon[16] presented his experiences with this method, both diagnostically and therapeutically, and reports most favorably on it. His paper was thoroughly discussed and those familiar with the method appear to endorse it most strongly.

Finally, Crohn, Reiss and Radin[17] have presented the results of their investigations into the premises upon which the rationale of this method is based and have taken exception to some of the views we have expressed. We welcome the appearance of such a paper because it reflects a true investigative spirit and an attempt at a logical interpretation of the experimental data which they collected. Their contribution is too long to admit of free discussion in this paper and so important as to require a detailed reply which will be published elsewhere. They, however, conclude this paper as follows:

"While we have not succeeded in utilizing the diagnostic test of Lyon for the identification of chronic gall-bladder disease we think that the subject is entitled to much consideration and thought."

We believe that now sufficient water has run under the bridge to evaluate the position that this method of non-surgical biliary drainage occupies today and to further predicate our views as to certain possibilities it possesses for future endeavor. To this end we have undertaken an intensive study of 100 consecutive cases of gall-tract disease observed in private practice, starting from a period when the technic of this method had become perfected and carrying each case through a proper length of time so that it might be judged fairly on its own merits as an individual case.

The records of these patients were very carefully analyzed from 305 tabulated points of view, embracing etiology, symptomatology, physical examination of the entire gastro-intestinal tract and the common routine and various special methods of clinical examination. Thirty-one of them were studied by the roentgen ray and 35 of them by a careful review of the findings of previous abdominal laparotomies, 17 of which were operations or reoperations upon the biliary tract itself. These 17 laparotomies represented gall-tract operations done on 12 patients, 4 of whom had been operated upon twice and 1 patient three times, and all 12 of them were complaining bitterly of symptoms still referable to the upper right quadrant. Eight of these 100 cases we referred for operation or reoperation upon the gall tract and in each one our preoperative diagnostic findings were confirmed in detail. Twenty-two of them had had their appendices previously removed. Finally all were studied and restudied in the light of the direct evidence furnished by the cytology, chemistry and bacteriology of the bile and the manner of its delivery into the duodenum and by the reactions on the individual patient of this non-surgical method of biliary drainage. These various procedures provided the planks in the diagnostic platform. Ninety-four of these 100 cases were carried through a course of treatment by us and these cases particularly were critically analyzed and, where there was any reasonable doubt, the end-result was entered against us as being unsuccessful rather than successful.

We propose in this paper to point out some of the lessons we have learned in regard to the importance of securing certain historical, physical, laboratory and technical data as a necessity in properly diagnosing and classifying cases of gall-tract disease (with or without complications) as a first step in a decision for or against their management by surgical or non-surgical methods; to point out some of the lessons we have learned both for and against the therapeutic effectiveness of non-surgical biliary drainage; to point out some of our impressions both for and against the effectiveness of surgical procedures as examplified in the cases studied, and, finally, to present some of our views as to future problems of biliary-tract disease which must be worked out.

In a critical study of the very excellent paper by Cheyney[7] on the "Diagnosis of Gall-bladder Disease" we were very much impressed

with the favorable case he (entirely unwittingly) made for the value of our method of studying the upper right quadrant group of patients by duodenobiliary drainage, as one of us has previously advocated. Any impartial reader of Cheyney's paper will probably realize that he has truly stated the facts in regard to his classification of his first three groups, based upon a diagnosis determinable alone upon a carefully taken history, physical examination amplified by the roentgen ray and the simpler routine laboratory studies of the stomach and the stools.

Permit us to quote from and comment on a paragraph from this paper. He says: "Thus in Group 1 of gall-bladder histories *recurring attacks of biliary colic* (italics are our own) characterize the story, with good health between. In Group 2 stomach symptoms play a prominent part but the *colic attacks* (italics are are own) still form the diagnostic featrue. In Group 3 the stomach symptoms preponderate, *colic* (italics are our own) has disappeared and the gall-bladder symptoms have quieted down to minor importance."

Comment. These cases are all manifestly *late* cases in the sense of having already reached the formed calculus stage as demonstrated operatively in the finding of gall-stones in each of the illustrative cases Dr. Cheyney has selected or they are *late* cases in the association of formed pathology, such as thickened gall-bladder or duct walls, inflammatory adhesions or involvement of the pancreas, duodenum and their lymph nodes. *These are the easy gall-bladder cases to diagnose and they are easy because we diagnose them too late to accomplish anything except by surgical measures at some risk to the patient and often too late to permit the surgeon to apply corrective surgery which will be permanent in its good results for the patient.*

Cheyney further says, "In Group 4 there are no symptoms but those produced by the stomach, over months or years, and the gall-bladder speaks only vicariously, calling no attention directly to itself."

Comment. This is the important group to recognize in this stage of precalculous formation and prepathology. We must learn to diagnose this group if we desire to advance our present status of management of gall-bladder disease, and we can learn to do so by utilizing the intimate and direct diagnostic measures which have been emphasized in earlier papers and not wait for the months or years to pass during which stones are forming and inflammatory adhesions being developed. *Diagnosed at this stage many cures can be accomplished therapeutically by this method without having later recourse to surgery.*

Finally, Cheyney says: "There should really be a Group 5 described where the gall-bladder contains stones but gives rise to no symptoms of any kind until either some sudden attack of pain or operation performed for some other ailment reveals cholelithiasis.

But these cases sooner or later develop symptoms that put them into one of the four groups described, and they cannot be diagnosed until they do."

Comment. With this we would like to emphatically disagree. They can be diagnosed, but not by the analysis of the history or the physical examination, not by the forty-five minute test meal extraction nor by the roentgen-ray examination unless it is unequivocally positive. This group of so-called quiescent stones is necessarily also a late stage which has gone entirely unrecognized in its formative period, and we believe many cases of this group, as well as of Group 4, may in the future be included in the class of *preventive medicine* if more patients were routinely studied and treated by this method. Certainly all cases which give in their histories suggestive etiological factors such as typhoid fever, influenza, chronic bronchitis, tonsillitis recurrens, chronic nasopharyngitis, sinusitis or oral sepsis should have such a study made. Also those patients require such a study who give a history of catarrhal jaundice and also perhaps more particularly, those who have a progressive brownish pigmentation of the skin and who frequently show some jaundice of the sclera and of the hard palate or who may have the spider-web like tracings of capillary anastomoses of the collateral portal circulation just above the costal margin or who may have multiple telangiomas. This group of cases is too frequently overlooked and the skin pigmentation will be frequently found due to chronic poisoning from static bile within the gall-bladder or within the smaller bile ducts around the liver lobules or due to poisoning from the waste products filtered out from the portal circulation by the liver and excreted in the bile; but poisonous products which are again reabsorbed into the portal system and carried back to a liver whose cells are becoming more and more fatigued by the endless load thrown upon them until they ultimately fail to secrete a bile normal in its chemistry. Among this group will be found many cases of migraine, with or without biliousness, who have become victims of cholagogue laxative habits. Many cases of unsuspected duodenitis and of ileocolitis and sigmoiditis are among this group, as well as many cases whose appendices have been removed but who still continue to complain of gastro-intestinal dyspepsias of vague and nondescript types. Here, too, lie many cases of chronic visceroptosis with static bile from partial obstruction due to traction on supporting peritoneal attachments in the upper right quadrant. We believe that many of these types of cases may be like those found in Cheyney's fourth and fifth groups. Most of these cases *can* be diagnosed as having biliary tract disease, but only by an intimate study of the chemistry, physical properties and the cytology and bacteriology of the gastroduodenobiliary fluids when analyzed with and balanced against the evidence or data obtained by history and physical and laboratory examinations. It is not so difficult but that it may be mastered by any clinician who maintains a properly functioning workshop.

We trust that Dr. Cheyney will understand that the above comments are not intended in any sense as derogatory to him. His paper enhances his reputation as an able clinician. We feel that these comments are necessary to drive home the point of the great need of establishing earlier means of correctly diagnosing gall-tract disease, thereby giving us a better chance to throttle it in its infancy rather than in the old age of its life-cycle. This we firmly believe is possible by the careful and painstaking application of this method.

In our series of 100 consecutive gall-tract cases so studied we found 27 per cent of clean-cut gall-bladder syndromies, 4 per cent of gall-stone syndromies, 22 per cent of a mixed syndrome (gall tract, duodenum, appendix and colon), whereas 47 per cent presented only a vague atypical dyspepsia with or without biliousness. Eighty-eight per cent of these 47 cases showed an unsuspected masked infection of the duodenobiliary zone, among whom 50 per cent showed streptococcic infection. Of these 100 cases 32 of them could have been readily diagnosed as gall-tract disease if studied only in the light of the history and physical examination, supplemented by roentgen-ray examination and by our usual gastro-intestinal methods; whereas 68 per cent of them would have failed of such diagnosis except by means of direct cytology, bacteriology and chemistry of the bile.

Here, then, is one lesson in diagnosis we have learned, and that the diagnoses were correct was proved by the subsequent results of the plan of treatment employed. It is not our purpose now to go into the minutiæ of diagnosis which has been emphasized in previous papers, but rather to present the field of treatment by duodeno-biliary drainage and some of the lessons it has taught us.

We rather take it for granted that most of you are aware of the inception and development of this method of more intimately approaching the diagnosis into diseases and disorders of the biliary tract and that you are now familiar with the possibilities of treating successfully by this non-surgical method of biliary-tract drainage many of the earlier and some of the later states of gall-bladder and duct disease.

Merely to refresh your memories let me recall to you that the fundamental basis of this method springs from the discovery of the late Professor Samuel J. Meltzer,[1] of the Rockefeller Institute, of the fact that a solution of magnesium sulphate when introduced locally into the duodenum will relax the tonus of the duodenal wall and the sphincter (Oddi's muscle) of the common bile duct, and that almost simultaneously with this relaxation the gall-bladder will expel its fluid contents, partially or wholly, into the duodenum. In previous papers one of us has pointed out the usual sequence of bile flow from the various components of the biliary system, and the method adopted for the recovery of this fluid for chemical, bacterio-

logical and cytological examinations relative to developing a new method of detailed diagnosis and as a direct check on the progress and efficiency of treatment.

It is now our privilege to come before this meeting and declare more positively our belief that it is now possible by this non-surgical method to drain the gall-bladder and biliary ducts of their fluid contents, within certain limits, to which attention has been called in previous papers. In the last of these papers thus far published the scope of this method was summed up as at present developed, first as a *means of diagnosis* of biliary diseases to supplement the usual clinical methods of diagnosis and help given us in many cases by the roentgenologist; secondly, as *an alternative method of treatment* of many types of gall-bladder and duct disease in which there arises a question of opinion as to whether surgery is or is not emphatically and immediately indicated; and, thirdly, as *a supplementary method* of postoperatively continuing the surgical principles of drainage in those cases incompletely cured by surgical means alone.

As a result of four years of practical application of this method of diagnosis and treatment of biliary-tract disease in a series of over 400 cases,we can most earnestly express our belief that it is now a proved and rational method in the successful treatment of early cases, and is possessed of great possibilities of future development in the prevention and control of many of the later and more severe states of disease of the biliary tract, and we trust it may hopefully be extended to certain diseases of the liver, of the pancreas and of some of the more serious of the problem diseases of internal medicine. Future papers will be devoted in part to a discussion of some of the results of an extension of this study into this larger field.

At this time we will not enter into a discussion of the principles and method of draining the gall-bladder except to have you refer briefly to this chart of the biliary system which hangs before you. We believe that the sphincter of Oddi normally is closed during the inter-digestive phase and that it opens in response to the stimulus of food chemistry. Then according to the law of contrary innervation propounded by Dr. Meltzer[1] the gall-bladder empties itself partially or wholly of its contents. The volume of bile expelled by the gall-bladder most probably depends upon the state and composition of gastric food chemistry reaching the duodenum if the experiments of Rost[18] are correct. It is by studying the departure from the normal physiological sequence of events, as seen to follow the local application of magnesium sulphate to the duodenum, as well as by a study of the gross and microscopic appearance, the bacteriology and the physiological chemistry of the recovered bile, that we arrive at definite conclusions relative to the state of the biliary apparatus, both as regards its physiology and pathology.

The first angle from which these cases were studied was from that

of previous operation. It was found that 35 cases had been abdominally operated on prior to the present study. Of these 12 had undergone gall-bladder surgery, 9 of them accompanied by appendectomy and 13 had had appendectomies independent of this gall-bladder surgery. After reviewing the 12 postoperative cases of gall-bladder surgery to determine residual infection it was found that positive bacteriology could be demonstrated in the biliary tract in 62 per cent of the cases in which a cholecystectomy had been done and in 100 per cent of the cases in which cholecystostomy had been practised. In this small series, then, it would seem that cholecystectomy is the operation of choice, considering only for the moment the question of residual infection. From the above it will be seen that surgery in the first place failed, in a too large percentage of cases, to free the biliary system of infection; and, in the second place, either failed to remove the primary focus causing multiple secondary foci or failed to recognize the early stages of biliary-tract infection and proceeded to remove the appendix alone.

The next point considered in our study was the question of attempting to find the primary source of the infection which had caused the gall-tract disease. We have felt for a long time that infection in the upper respiratory and digestive tracts is very frequently responsible for many of the acute or chronic conditions in the tract below. The six principal points of primary focal infection we found to be in the tonsils, gums or teeth, the posterior nares, sinuses or the bronchial tree. The five principal secondary foci are the stomach, the duodenum, the gall-bladder, the appendix and the rectosigmoid colon. These may be involved singly, all together, or in series, but surgical or medical treatment directed to any one of them alone will not preclude a recurrence or later development of trouble at one of the other sites unless the primary source of the infection is eradicated. Reviewing our operated group of patients from the standpoint of present or previous infection we found that in the 12 cases previously operated on we are able to demonstrate, by cultural methods, infection still present in the gall tract in 9 cases. Of the 12 cases we found that 10 of them, in addition, showed pathogenic focal infection in the tonsils, teeth or sinuses. Of the 4 other cases whose biliary tract had been previously been operated 1 of them was an exploratory cholecystotomy alone and 3 were for the release of gall-bladder adhesions alone. Here, of course, there was no surgical attempt to remove infection and therefore these cases must be excluded from this angle of analysis. Of 84 cases whose biliary tract had not been previously operated upon we could classify all of them as having various grades of cholecystitis, and that 24 of these 84 cases gave evidence by the tuning-fork or by roentgen-ray examination of the presence of adhesions. Lastly, 14 cases could be classified as having gall-stones in an active or quiescent stage. Analyzing our 84 cases

of non-operated gall-tract disease for residual focal infection we found 39 showed abscessed or suspiciously capped teeth; 29 cases had infected tonsils; 18 cases had pyorrhea; 17 cases had postnasal discharge, 3 of which were proved sinus infection; 6 cases had chronic bronchorrhea; and 4 cases had chronic otitis media. Several of these cases combined two or more points of infection.

We will not confuse you with figures relative to a discussion of the associated functional disturbances of the gastro-intestinal tract found in the series of patients, except to say that in the 14 cases of proved or probable cholelithiasis 57 per cent showed the gastric acidity by the fractional method either markedly reduced or absent and 21 per cent showed hyperacidity; but in those cases in which gall-stones could be reasonably excluded we found the gastric acidity reduced in only 34 per cent and absent in none, whereas 41 per cent in this group showed hyperacidity. In this respect our study confirms the findings of other investigators who have formulated a belief that a normal or increased acidity is a laboratory datum supporting a clinical assumption of cholecystitis as against cholelithiasis. This is in accord with the experimental evidence of Rost that the best normal physiological stimulus to the discharge of gall-bladder bile lies in a gastric chemistry rich in proteose, peptones and albumoses. Such conversion is only afforded by a normal or increased gastric juice. Therefore in the subacid or anacid gastric states the gall-bladder bile is more liable to become static and crystals are thrown out of solution. This is the potential stone or precalculous state. If mucosal inflammation or infection be added the formation of gall-stones is accelerated.

Analyzing the possibility of multiple infection of the gastro-intestinal tract we found that 22 patients who had previously had their appendix removed (9 of which were in conjunction with biliary-tract surgery) still showed evidence of residual infection of the gall tract; that 21 cases gave clinical evidence of appendicitis with proved infection of the gall-bladder; that 3 cases showed a lesion of the gall-bladder associated with duodenal ulcer; and that 4 cases suggested associated lesions of the gall-bladder, the duodenum and the appendix. A good many of these cases, also, had inflammation of the rectosigmoid, but were not specifically tabulated.

The question of the significance of biliary regurgitation into the fasting stomach is one that has always interested us and we have come to feel that *frank* biliary regurgitation is evidence of a disturbed physiology of the duodenobiliary mechanism. In the first place we believe the sphincter of Oddi should be closed except during the digestive cycle, and, in the second place, that reversed peristalsis should not occur normally in the fasting duodenum with certain exceptions not to be discussed here. In this study we found that of the cases with previous gall-bladder surgery 71 per cent showed both fasting and digesting biliary regurgitation as against

47 per cent of fasting and 23 per cent of digesting regurgitation in the non-operated cases. From this it would seem that operation on the gall-bladder very definitely disturbed the physiology of this segment of the gastro-intestinal tract. In addition it has been proved experimentally on animals, and by clinical experimental study of these postoperative gall-bladder cases, that surgery in each instance has destroyed the contrary innervation of the gall-bladder and Oddi's sphincter and has changed the normal physiologically intermittent discharge of bile into the duodenum into a pathologically continuous one, with, in many instances, harmful results, notably a severe and intractable diarrhea. All of this series of patients had complaints referable to the gastro-intestinal or biliary-tract systems, but, in addition to these localizing symptoms, a very large number (approximately 50 per cent) gave a history of symptoms suggesting focal infection or of autointoxication, the most prominent being easy fatigue, nausea, headache, dizziness and backache. In 54 of these 100 cases the physical findings in the upper right quadrant were entirely negative; in 46 definite tenderness, muscle spasm or rigidity could be demonstrated. There was no instance of palpable gall-bladder in the series. The average duration of ill health in these patients was eight years. Of this whole series positive bacteriology was demonstrated in 93 cases; the material obtained was sterile in 4 cases and no material was obtained in 3 cases. Of the 93 cases with positive bacteriology the streptococcic group was isolated in 50 per cent, staphylococci in 25 per cent, Bacillus coli in 15 per cent, Bacillus subtilis in 8 per cent, Bacillus pyocyaneus in 1 per cent and Bacillus typhosus in 1 per cent.

We would allude to one other fact brought out from our study, and that is the importance of recognizing catarrhal inflammatory or infected states of the duodenum, independent of duodenal ulcer or adhesions. These states are much more commonly present than is usually realized and have great significance in the causation of vague or atypical dyspepsias, and are conditions which often precede the later states of better developed pathology and a better understood symptom-complex. We found in our series of cases that 56 of them gave evidence of duodenitis, either simple catarrhal or with unusual exfoliation of duodenal epithelium, that 25 of these 56 cases gave evidence of bacterial infection of the duodenal mucosa and that 3 of them were infected with the Lamblia (or Giardia) intestinalis recoverable by tube in the living state. Obviously the diagnosis of these states of duodenitis can be made more accurately by the direct examination of the duodenal fluid than by any of the indirect methods.

To sum up the foregoing the final diagnosis in these 100 cases, based on a careful analysis of the history, physical examination, various special examinations and the detailed information derived from a diagnostic non-surgical biliary drainage, were divided as

follows: Gall-bladder syndromes, 27 per cent; gall-stone syndromes, 4 per cent; mixed syndrome (ulcer, appendix, gall-bladder), 22 per cent; and vague atypical dyspepsia (with or without biliousness), 47 per cent. There was "masked" infection, proved by culture, in 88 per cent of the cases. If, however, these cases had been studied only by the usual gastro-intestinal methods, supplemented by analysis of the history, physical examination and the roentgen ray, but without the added information derived from biliary drainage, only 32 per cent could have been diagnosed readily as gall-bladder cases. The remaining 68 per cent were impossible of such diagnosis except by means of direct cytology, bacteriology and chemistry of the bile.

To turn next to the question of treatment, 94 of these cases were treated by us. In all cases but one the chief therapeutic measure consisted in lavage and disinfection of the stomach followed by drainage of the biliary apparatus. The duodenum was then disinfected as a measure of local protection and a duodenal enema of Ringer's solution was given, reinforced where necessary with sodium sulphate, in order to secure a free fluid evacuation promptly and thus sweep out of the intestinal tract such infected bile as failed of recovery in our bottles. The duodenal enema of 250 cc is kept at 103° F. and allowed to drip in slowly in not less than twenty minutes. This whole procedure requires from two to three hours. Colonic irrigations were used only in exceptional cases where indicated. Rectosigmoidal insufflation, after Soper's methods gave us much better results.

As the individual necessities of each case demanded, other indirect therapeutic measures were combined with this direct topical treatment. Medicine was given by oral, subcutaneous, percutaneous and intravenous routes. The only oral medicines used were digestive substitution products and hepatic secretogogues. Electricity, dietetics, glandular therapy, hygiene, psychotherapy, exercise or rest were prescribed in certain cases.

But the first bulwark of treatment was our insistence on topical treatment of the stomach, duodenum, biliary tract and colon. The second agent in which we placed most reliance was the autogenous vaccines. Especially were these useful when they gave rise to a specific focalizing reaction reproducing one or more of the presenting symptoms, and those cases in which they occurred averaged better in their results. Among 58 cases receiving autogenous vaccines there were 17 who gave an unsolicited history of focalizing reactions simulating one or more of the chief complaints. Among these gall-bladder pain or soreness was mentioned 13 times and migraine was mentioned 5 times. Pain in a tooth socket following a vaccine of streptococci obtained from the gall-bladder and from the apex of a tooth root in 1 case. Pain in the tonsillar fossæ following a vaccine of streptococci from gall-bladder and tonsil in 1 case; soreness in

the appendiceal region was mentioned once; and increased joint involvement in a case presenting arthritis was mentioned once.

In summarizing the results of treatment by this method in this series of 94 patients we find that 73 of them showed complete arrest of symptoms (symptomatic recovery), 17 showed partial arrest of symptoms (improved) and that 4 of them were unimproved. But checking up from the objective standpoint, based upon a direct examination of the bile, we could demonstrate a complete return to normal findings in the bile in 47 cases, while 35 patients still showed abnormalities of the bile. On 12 patients there was insufficient data on this point to classify them, showing the need of correcting our errors of omission. As we were reviewing the results of treatment we noted the discrepancy in that 73 patients showed a complete symptomatic recovery, and yet in only 47 patients were we able to demonstrate a complete return to normal objective findings in the bile. This has indicated to us the inadequacy of considering simple arrest of symptoms as the criterion of a cure and emphasizes the need of continuing the treatment faithfully until the pathological findings disappear; otherwise relapse is extremely likely to occur. Again it was interesting to observe that as treatment was continued the complete improvement in findings ran more nearly parallel to the complete arrest of symptoms, and this, and this only, should be made the criterion of a real cure. Eight of these patients were diagnosed and treated non-surgically for a short period and then referred for operation, and were then again postoperatively treated by us. All of these patients, except one, made complete recoveries. Postoperative drainage, with protection of and treatment of the duodenum and intestinal tract, we believe to be a most important prophylactic measure to guard against relapse. Finally it was instructive to us to learn that of the 17 cases who complained of focalizing vaccine reactions 90 per cent had complete relief of their symptoms as against 77 per cent for the entire series; and, furthermore, 76 per cent showed complete return to normal findings against 50 per cent for the entire series. Hence our faith has grown in the efficiency of autogenous vaccines when properly selected by repeated culture checks, when properly prepared and properly administered, and particularly so when they give rise to focalizing reactions reproducing a presenting complaint.

In order to illustrate some of the lessons learned in the study of this series of patients, we will present briefly some of the case reports with a few words of comment.

Mr. F. S. W., aged thirty-seven years, was referred to us on June 9, 1920. With the exception of an attack of slight jaundice in 1900 and a tendency to recurrent tonsillitis prior to 1903, at which time his tonsils had been presumably removed by a tonsillotome operation,

this patient had enjoyed robust health until he suffered a severe attack of pandemic influenza in October, 1918. With this he was for five weeks very sick in bed. It was complicated by bronchopneumonia and cardiac insufficiency, which prolonged a slow convalescence through several months. In April, 1919, he had an attack of what was called "trench mouth," with spongy, bleeding gums, which lasted for one month. In March, 1920, he was told he had "acidosis," and had been given large doses of milk of magnesia, which he has continued to take for the past three months, with the result that his bowel movements have become very loose, contain slimy and shreddy mucus and are rather foul-smelling. In one year he had decreased in weight from 182 to 155 pounds, although he stands six feet two. His chief complaints were progressive weakness, a sense of nervous gripping in the right epigastrium, followed by a sense of "empty pain" about one hour after meals, sometimes wearing off spontaneously, but always made temporarily better by eating. He also complains of rectal tenesmus.

Physical examination disclosed numerous foci of infection as follows: The tonsils were inflamed and boggy, enlarged and cryptic, and pus could be readily expressed from both of them, smears from which recovered streptococci in abundance. Roentgen ray of his teeth showed three well-defined abscesses. His stomach examination disclosed a definite infective catarrhal gastritis, with a high normal secretion and motility retarded intermittently by pylorospasm. His duodenal cytology showed a moderate catarrhal and exfoliative duodenitis, and drainage of his gall-tract demonstrated a well-marked and exfoliative cholecystitis and choledochitis with masked infection. Cultures from his "B" bile recovered a hemolytic streptococcus. His gall-bladder discharge ranged between 90 and 150 c.c. of static, green-black, slightly turbid bile of increased viscosity, and contained large numbers of mucopus flocculations. The microscopy of this showed much bile-stained columnar epithelial exfoliation, numerous pus cells, a large amount of precipitated bile salts and cholesterin crystals and numerous colonies of bile-stained cocci. As a result of this inflammatory state we found the common duct uniformly open in the fasting state without the use of magnesium sulphate. This we believe to be evidence of disturbed physiology which may be functional or associated as a reflex to pylorospasm, appendicitis and colitis, but which occurs much more commonly when there is a duodenitis or inflammation of the gall tract.

He presented historically the symptom-complex of duodenal ulcer, but which, in the absence of specific laboratory and roentgen-ray confirmation, we have come to recognize as our mixed syndrome, which may be functional pylorospasm, duodenitis, duodenal ulcer, cholecystitis, appendicitis and, rarely, ileocolitis, with special involvement of the rectosigmoid. He gave, however, no direct clini-

cal, historical or physical findings that suggested gall-tract disease other than his attack of catarrhal jaundice twenty years previously. In addition, on examination we found a suspicious tenderness in the region of his appendix or cecum and an inflamed or spastic sigmoid. His blood showed a moderate secondary anemia with a negative Wassermann. His pulmonary, cardiac, renal and endocrine systems were relatively normal, but his nervous system was distinctly under tension, with a disturbed sleep picture of involuntary twitchings and a tendency to fantastic nightmares.

Here, then, was the picture of disseminated infection of the gastro-intestinal tract, most probably emanating from the tonsils and contributed to by the infection at his tooth roots, and, with his general resistance materially broken down by the severe type of influenza, with its complications, through which he had passed, we find his mucosal surfaces a fertile ground for the transplantation of the streptococcus.

As a first step in his treatment we had his tonsils removed and cultured and a vaccine was made from the hemolytic streptococci recovered from them, mixed in equal amount with the same organism grown from his gall-bladder bile. The similarity of growth of these streptococci in various media suggested them to be of the same strain. Two of the three teeth showing apical abscesses were extracted in Boston (no culture being made, unfortunately) and the sockets treated. He was then given a duodenobiliary drainage with a duodenal enema twice a week, together with a vaccine injection and iron citrate, sodium cacodylate and sodium glycerophosphate subcutaneously. His symptomatic response was prompt and his recovery was progressive. After seventeen such treatments he had gained fourteen pounds (from 155 to 169) and was called back to Boston by business and was referred into the care of Dr. Franklin W. White, who continued his treatment at greatly increased intervals. During our observation of him his abnormal findings in the duodenum and gall tract had progressively improved, and on December 31, 1920, Dr. White writes: "The last bile drainage was done on December 22. The bile was a very clear green-yellow with nothing abnormal in the sediment. He is feeling entirely well and has gained steadily from 169 to 186 pounds, which he weighs today." Six months later this patient still remains perfectly well.

Comment. This case represents a severe type of disseminated infection of the gastro-intestinal canal, with a masked lesion in the gall-bladder in the early stage, in which the symptoms are more suggestive of a pyloro-duodenal ulceration rather than involvement in the gall tract. It illustrates the importance of early diagnosis by the differential methods we have advocated. Later on the symptomatic picture will change and may call attention to the gall-bladder, but often by that time the pathology is extensive. This case finally teaches us that we may achieve excellent results

and may prevent the necessity for later surgery in many cases; but we must start our treatment by removing all recognizable foci higher up in the tract and then energetically treat the condition itself by topical and direct methods. We have 18 other cases in our series of 100 studied and treated who may be classed in this group.

Miss E. B., aged forty-three years, referred to us on July 11, 1920, had for ten years been suffering from severe prostrating migraine attacks which occurred in somewhat definite cycles every ten days to two weeks. She had tried out a great many remedies for relief of these sick headaches, with apparently no improvement.

She gave a history of absolutely no preceding infections in her past life except a stuffiness and catarrh in the left Eustachian tube, which has been under constant treatment by a most excellent specialist, with distinct improvement, and yet showed a tendency toward relapse.

On very careful physical examination she had absolutely normal findings in her eyes, nasopharynx, bronchial tree, lungs, heart, kidneys and pelvic organs. Her gastro-intestinal studies were likewise negative except for the particular findings in the gall-bladder and duodenum, which will be mentioned later. She had had constant and progressively more obstinate constipation for many years and represented a typical constipation-laxative habit vicious circle.

She states that the migraine attacks come almost without warning, with no causative factor to which she can ascribe them. They last from two to four days of intense prostrating "sick" attacks, and when at the worst are always accompanied by dry retching and terminal vomiting of bile, which usually brings the attack to a close. She has temporary relief in the use of cholagogues, especially calomel and salts. She describes the attacks as beginning with a "thick" feeling in the head, followed by pain which is first felt over the right eye and radiates down the temple to the right mastoid region. Less frequently the pain is felt, also, over the left orbital region, with the same distribution. This may be due to the influence of Arnold's auricular branch of the pneumogastric nerve. The abdominal physical findings were entirely negative, although special attention was paid to the gall-bladder region.

No direct diagnostic evidence could then be furnished from her examinations, which pointed toward the gall-bladder, except the historical data of recurring bilious attacks associated with migraine and the further fact that she had been noticing a progressive brownish pigmentation of her skin, which had been definitely deepening during recent years.

Her duodenobiliary drainage examinations supplied the necessary diagnostic data, for we found the gall-bladder bile to be static, inky-black, with increased viscosity and mucosity, and delivered inter-

mittently in the manner of the atonic flow previously described, and infected with a Streptococcus viridans and Bacillus coli. In this "B" bile was found a large amount of flocculent sediment, the cytology of which showed marked exfoliation of tall columnar, bile-stained gall-bladder epithelium, with much amorphous bile salts, cholesterin crystals, pus cells, spiraled strands of mucus and bile-stained bacteria in the colony formation representative of true infection.

Her treatment consisted of duodenobiliary drainage, followed by duodenal enema twice a week for two weeks, then once a week for a month, then twice a month for a period of three months. Autogenous vaccines were given every five to seven days and caused a focalizing reaction reproducing the migraine. With the exception of pancrobilin nothing else was used for her constipation.

The result of this treatment showed steady progressive improvement both in symptoms and in the objective findings in the bile. The migraine attacks became of lighter and lighter severity and of decreasing frequency, and she noted a general systemic improvement in her increased alertness, power of concentration, better sleep states, increased amount of vigor, and especially notable to her was the progressive absence of her sense of daytime drowsiness and the rather remarkable clearing of the brownish pigmentation of her skin and improvement in her complexion.

She has recently been seen and reëxamined and has had no headache for a little over four months, and says she feels splendidly well. She had had no bilious attacks; her skin was clear and showed practically none of the earlier pigmentation; her bowels were moving once daily and naturally, without any laxation; and her biliary drainage showed an absence of all the direct evidence recorded above upon which her diagnosis had been based.

(To be continued in February issue.)

VISCERAL ADHESIONS AND BANDS; NORMAL INCIDENCE. A PRELIMINARY REPORT.[1]

By John Bryant, M.D.,
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The material which is the basis of this paper was obtained before the World War incidental to a much more comprehensive investigation into the etiology and treatment of the chronic intestinal invalid.

[1] Read at the Annual Meeting of the Gastro-enterological Association, Boston, June 6, 1921. Original data for this article was obtained in 1912–1914 through the courtesy of Professors Pick and von Hanseman, of Berlin, Professor Fränkel of Hamburg and the students then working in their pathological institutes.

Its presentation has been delayed for several years, but there does not in the meantime appear to have been published any data which considers the question of visceral adhesions or bands from the same points of view.

The literature upon adhesions which is based upon reported facts is scanty, contradictory and inadequate. Although early writers frequently mentioned the existence of adhesions or bands within the abdomen, modern scientific literature upon the subject may be said to date from the exceedingly instructive paper by Virchow,[2] written in 1853. Virchow not only discussed the question of adhesions in the adult, but recognized that such abnormalities were occasionally found in the fetus, and referred to the fact that some of his contemporaries or predecessors had attributed these variations in the fetus to intra-uterine peritonitis. Since the time of Virchow, however, surprisingly little in the way of accurate data has been presented, the majority of recent writers having considered adhesions largely from a surgical point of view, and even then usually on the basis of personal opinion rather than of published facts.

One of the most valuable of such papers, from the surgical point of view, is that by Morris, in[3] which, although no actual data is given, he divides adhesions into four groups in the following order of frequency: (1) Gall-bladder, (2) cecum and appendix, (3) sigmoid and (4) pelvis. Robinson,[4] in 1896, reported observations based upon a variable number of cases, from 40 to 150, tending to show that the viscera most frequently involved were, in their order of frequency, the spleen, mesosigmoid, pelvis, cecum and appendix and gall-bladder. Opitz[5] reporting upon a series of 160 cases examined in 1914 agreed in general with Robinson, placing the sigmoid first in frequency, followed in order by the cecum and appendix.

There are also available a few studies of special areas, again mostly from a surgical point of view, of which by far the most reliable is the recent one by Smithies,[6] reporting on gall-bladder adhesions in a series of 1000 operative cases. In general, it may be said, however, that there has been practically no serious attempt made to study adhesions from the point of view of sex and progressive age or from the point of view of the normal occurrence of adhesions in unselected material.

It is believed that the present paper will to some extent supply this deficiency, since it is based upon a series of over 1000 observations upon 297 unselected consecutive postmortem cases of all ages and both sexes, the only cases excluded being those few recently postoperative or those exhibiting recent frank peritonitis.

[2] Virchow's Arch., 1853, **5**, 281.
[3] Tr. Am. Assn. Obst. and Gynec., 1906, **19**, 223.
[4] New York Med. Jour., 1896, **63**, 101.
[5] Deutsch. Gesellsch. f. Chir., 1914, **43**, **2**, 107.
[6] Jour. Am. Med. Assn., 1918, **71**, 1804.

In the obtaining of the original data, on the one hand every attempt was made to secure accuracy, the original notes on one case being written immediately after the completion of the examination and before proceeding to the examination of any subsequent case. On the other hand attempt was made not to overlook any variations from the accepted normal.

The data having been obtained they were next divided for purposes of study into male and female groups. After further study these groups were again subdivided into age periods as follows: fetal, birth to two years, two to ten years, every decade from ten to seventy years and a senile group composed of those cases seventy years of age or over. Although when thus subdivided the number of cases in each age group averaged only about 20, being from this point of view unsatisfactorily small, yet it was possible from this original subdivision to observe certain general tendencies which were largely substantiated by dividing the male and female groups into only four subgroups. These subgroups were: fetal, birth to forty years, forty years to senile and senile. At later stages of study these four groups were again frequently condensed into two, the group below forty years of age and the group above forty years of age.

It has been generally considered that where adhesions are found in the fetus, they are the exception and not the rule. This is not correct and even recent attention which has been given the question of developmental bands fails to take into consideration the extreme frequency with which such abnormal adhesions or bands occur within the fetal abdomen.

A careful study of the data available showed that there were only 8.9 per cent of 180 male cases of all ages in whom adhesions were absent; in other words, adhesions were present in 91.1 per cent of these 180 male cases. In this male group there was a total of 65 different adhesions or bands. Examination of the male fetal group showed that 100 per cent of 18 cases presented abnormalities; in other words, no male fetus was free from some form of abnormal adhesion or band.

In the female group of 117 cases of all ages there were but 14.5 per cent in whom adhesions were absent; in other words, adhesions were present in 85.5 per cent of these cases. In this female group there was a total variety of 57 different adhesions or bands. Examination of the female fetal group showed that adhesions were absent in only 12.5 per cent of 16 cases; in other words, adhesions were present in 87.5 per cent of these female fetal cases.

An examination of the total number of structures involved according to age showed that there was practically no increase above the fetal rate in either sex until the age of forty years. In the male fetus there was an average of 3.2 viscera per case involved; in the female fetal group the average involvement was 2.9 organs per case. The actual percentage increase above the fetal rate in the male

until the age of forty years was *nil;* in the female under the same conditions there was an increase of only 3.4 per cent above the fetal rate. This contrasts markedly with an increase of 43.8 per cent above the fetal rate for the number of structures involved in the males of over forty years of age and with an increased involvement under the same conditions in the female of 51.7 per cent.

The actual number of variations, in type of adhesions present in relation to the given age periods, shows a striking similarity to the figures just quoted, with the single exception that the sudden increase occurs in the thirty-year decade rather than in the forty-year decade. In other words, in both sexes below the age of thirty less than eleven different types of adhesions were found in any one age group in either sex, the number varying only one or two points from the fetal rate. Above the age of thirty, on the other hand, there is in both sexes a striking increase of almost 100 per cent in the variety of adhesions present, and this increased variety tends still further to increase up to and including the senile group.

The complexity of adhesions present, or, in other words, the number of structures involved in any given adhesive process, shows an interesting relation to age, and the general variation runs uniform in both sexes. There is from the fetus onward a progressive decrease in the number of simple adhesions present in any age group; on the other hand there is a progressive increase with increasing age in both sexes in the percentage of complex adhesions to be found in any given age group from fetal to senile.

The actual adhesions or bands present show a most interesting uniformity in both sexes not only in the fetus but in older ages as regards percentage frequency. The order of frequency in 297 cases of both sexes for the seven most frequent actual adhesions is shown in the Table.

ACTUAL ADHESIONS OR BANDS PRESENT. PERCENTAGE FREQUENCY, BOTH SEXES.

Adhesions or bands.	Male per cent.	Female per cent.
Gall-bladder to the duodenum and the transverse colon	25.6	24.8
Gall-bladder to the transverse colon	17.2	9.4
Gall-bladder to the duodenum	15.5	17.9
Appendix to the peritoneum	15.0	5.9
Omentum to the ascending and the transverse colon	11.1	12.0
Ascending colon to the transverse colon	10.6	5.9
Duodenum to the peritoneum	6.7	10.3

Study of the fetal groups shows that in both sexes the adhesion most frequently occurring is the same as that at the top of the list in the Table; in other words, from the gall-bladder to the duodenum and to the transverse colon. The second most frequent adhesion

in the fetus of both sexes is that of the gall-bladder to the transverse colon. It therefore seems reasonable to assert that these two most frequent adhesions are in both sexes of congenital or developmental origin, presumably existing as unabsorbed portions of the free edge of the lesser omentum or ligamentum hepaticocolicum.

A consideration of the location of adhesions from the point of view of the four quadrants of the abdomen shows that not only in the fetus but in all older age periods in both sexes the right upper quadrant is by far the most often involved. The right lower quadrant and then the left upper quadrant follow next in order of frequency.

A consideration of adhesions from the point of view of the individual organs involved at varying ages in both sexes is reserved for a later presentation.

Conclusions. 1. The frequency of occurrence of adhesions or bands in the fetus of both sexes has been greatly underestimated. Of a group of 34 fetal cases of both sexes only 5.9 per cent were free from demonstrable adhesions or bands; 100 per cent of the 18 male feti showed such variations from the normal.

2. The adhesions present in the fetus are less varied in number and of a definitely less complex type than those found to occur in later life.

3. The age of forty is critical in both sexes. There is practically no increase in frequency above the fetal rate of involvement for the different viscera by adhesions until the age of forty. Beyond the age of forty there is a sudden increase of about 50 per cent in the involvement of the different viscera by adhesions in both sexes, the increase being somewhat more marked in the female than in the male.

4. The two actual adhesions or bands found to occur most often in both sexes at all ages are in their order of frequency as follows: (*a*) Gall-bladder to the duodenum and to the transverse colon in both sexes; (*b*) gall-bladder to the transverse colon in the male and the gall-bladder to the duodenum in the female. In both the male and the females fetus the two adhesions or bands most frequently found were: (*a*) Gall-bladder to the duodenum and to the transverse colon; (*b*) gall-bladder to the transverse colon. It would therefore appear that these two most frequently occurring adhesions or bands are of congenital or developmental origin.

5. The regions or quadrants of the abdomen most frequently involved by adhesions or bands in both sexes are, in their order of frequency, as follows: Right upper quadrant, right lower quadrant, left upper quadrant, left lower quadrant.

CERVICAL RIB, WITH A REPORT OF TWO CASES.

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The detection of supernumerary rib in the living dates largely from the introduction of the roentgen ray into medicine. While in the lumbar region the diagnosis of an extra rib is only of academic interest, yet in the cervical region the subject becomes one of the utmost practical importance. According to Beck[1] the literature does not contain a single case in which the lumbar rib has caused any discomfort whatsoever, although, as pointed out by Kammerer[2] in 1901, "Supernumerary ribs are much more frequently found attached to lumbar than to cervical vertebræ." There is no consistent data regarding the frequency of cervical ribs. Fischel, of Prague, reports that in routine necropsy examinations, covering a period of four years, the condition was found in 1 per cent of all bodies examined. Gruber was able to demonstrate 45 cases on 76 bodies studied, while Henderson,[3] of the Mayo Clinic, states that of 80,000 patients examined only 31 cases of cervical rib were recorded. However, it is well to remember that only a few have any symptoms whatsoever, as is shown by the 139 cases analyzed by Pelling in 1894, in which only 3 patients had clinical symptoms.

The first description of the condition was made by Hunauld,[4] in 1742, but it was first recognized in life by Cooper in 1818, while the credit for the first successful removal on a living subject goes to Coote (1851). An article by Streissler, in 1913, is conceded to be one of the most exhaustive papers on the subject, there being 297 references with reports of 200 cases of cervical rib. However, Le Double's monumental work on *Variations of the Spine in Man*, published in 1912 and including 543 cases, deserves special mention.

Between 60 and 70 per cent of all reported cases of cervical rib have been in females. The condition in the majority of cases is bilateral, but the rib on one side is usually much longer than its fellow. In general, according to Beck, cervical rib is double in 67 per cent of cases and single in only 33 per cent, but a completely developed anomalous rib on both sides is regarded as quite rare, although occasionally they may reach to the sternum. The first case we have to report is bilateral and the second is unilateral, with a slight exostosis on the opposite side. The seventh cervical is by far the most frequent vertebra involved, although occasional cases

[1] Jour. Am. Med. Assn., June 17, 1905, **44**, 1913.
[2] Ann. Surg., November, 1901, **34**, 637.
[3] Mayo Clinics, 1913, p. 623.
[4] Church, A.: Jour. Am. Med. Assn., July 5, 1919, **73**, 1.

have been reported of the sixth, fifth, fourth and third, and Jelliffe[5] also calls attention to cases reported by Thomas Murphy and Sherren, each having symptoms due to pressure on a cervical rib springing from the first cervical vertebra.

The exact cause of the formation of a cervical rib has never been given, although its embryological formation is clear. "Embryologically each cervical vertebra has a costal process which with the transverse process forms the costotransverse foramen. The cervical rib arises as a result of the abnormally great development of this costal process, which process is traceable on all the vertebræ and in the thoracic vertebra furnishes the normal ribs." (Henderson, Mayo Clinic.) Although the condition is a congenital one, rarely do the symptoms develop before the second decade. Several reasons have been advanced for this, although as yet there is no generally accepted explanation. Beck suggests that while trauma and such constitutional diseases as anemia, chlorosis, rheumatism, tuberculosis and scrofula apparently cause symptoms to appear; the loss of the fatty protective padding in these diseases is the actual causative agent. He states that "The tissues adapt themselves to the rib during the period of development and no discomfort arises where a certain amount of elasticity or yielding tendency of the tissues exist." Hirsch, in 1899, reported a case in which he believed the appearance of symptoms to be from a periostitis following direct trauma.

Gruber's classification is the one generally accepted and divides cervical rib into four classes, depending on their length:

1. A costal process increase not reaching beyond the transverse process. Cases under this group are not classed strictly as cervical ribs.

2. Extending beyond the transverse process, terminating in a free end or united to the first rib. The first case we have to report falls within this class.

3. A longer rib than in Class 2 and attached to the first rib by a ligament.

4. Complete ribs.

It has been repeatedly noticed that the symptoms produced are not definitely related to the size of the anomaly, as it is obviously the position and not the size that chiefly produces the symptoms. In general, the signs and symptoms may be divided into four divisions:

1. Hump-like prominence in the lateral cervical region.

2. The appearance of pressure symptoms, manifested by circulatory or nervous disturbances.

3. Superficial pulsations of the subclavian artery.

4. Cervical scoliosis.

[5] Jour. Am. Med. Assn., July 26, 1919, **73**, 288.

In the majority of cases the rib is palpable in the neck, and on this alone the case is usually diagnosed and referred to the roentgenologist for confirmation, although Law[6] calls attention to the fact that the symptoms of an adventitious ligament may so closely simulate a cervical rib that only the roentgen ray can differentiate in the absence of operation.

Whenever the anterior extremity of the anomalous rib reaches far enough forward, the subclavian artery and brachial plexus pass over the rib, in which instance symptoms of compression may occur at any time. Pressure symptoms may therefore be referable to pressure on the brachial plexus, on the cervical sympathetic, the pneumogastric nerve or the subclavian artery. The most common and usually the first symptoms to appear are neuralgic pain in the neck, spreading to the head, thorax, arms and forearms, usually in the region innervated by the ulnar nerve and nerve of Wrisberg, as it is generally the inner cord which is first implicated. A common complaint is "rheumatism in the arm," many of the cases being diagnosed "brachial neuritis." On examination one may find formication and numbness in hands and fingers with some loss of muscle power in the entire extremity, although the reaction of degeneration apparently is never present. The temperature of the affected arm is usually lower than that of the sound side. Other symptoms which Kammerer and Planet both mention as rather frequently observed in their cases are the inability to fully extend the arm at the elbow and the occurrence of hoarseness attributable to pressure on the recurrent laryngeal nerve. Occasionally sensory changes appear early in the form of zones of anesthesia and paresthesia, although usually these changes make their appearance quite late. The circulatory disturbances are usually manifested by a feeling of numbness or tingling of the whole extremity, while frequently there can be detected an obvious atrophy of the thenar or hyperthenar group of muscles. Extreme circulatory disturbances may occur, as in a few cases reported in which gangrene of the fingers and hand occurred.

The elevation of the subclavian artery by the supernumerary rib results in a palpable pulsation which may cause suspicion of aneurysm. Occasionally true aneurysm does complicate the picture, but, as mentioned by Korg, there is always the danger in removing the anomalous rib so complicated, that one may hasten the growth of the aneurysm. He therefore advises strongly against its removal under these circumstances. The occasional aneurysmal dilatation of an artery distal to a point of partial constriction is due to the fact that below the constricted point there are definite changes in blood-pressure and in the structure of the vessel walls. These changes have been experimentally produced by Halsted[7] by partially constricting arteries with aluminum

[6] Ann. Surg., October, 1920, **72**, 497.
[7] Surg., Gynec. and Obst., 1918, **27**, 547.

bands. He found the systolic pressure reduced and the diastolic increased, thus lowering markedly the pulse pressure. Histologically, Halsted and Reid[8] have shown that there is a definite atrophy or partial disappearance of the elastic tissue in the walls for a short distance below the constriction, which probably plays an important part in causing the dilatation.

The fourth sign is cervical scoliosis, which is a rather rare type of scoliosis, but whenever found suggests the presence of cervical rib. Streissler in his study of 200 cases found this type of scoliosis in 16 per cent, and it is generally agreed that these two conditions frequently coexist.

According to Barker,[9] when there is a firm mass in the neck the differential diagnosis lies between:

1. Inflammatory enlargement.
2. A true tumor.
3. Enlargement of the salivary, thyroid or lymphatic glands.
4. Aneurysm.
5. Esophageal diverticulum.
6. Cervical rib.

Generally, careful physical examination is sufficient to make a tentative diagnosis of cervical rib, which can be definitely confirmed by the roentgen ray. However, Barker, reporting a cervical rib in his own case, calls attention to the association of syringomyelia with this anomaly. He states with pupillary disturbances, anesthesias or severe neuralgias it may be difficult to decide whether or not syringomyelia coexists. He speaks of his own case as showing a disassociation of cutaneous sensation, there being a loss of tactile and thermal but a retention of pain sense, while the syringomyelia type shows a loss of pain and thermal sense, with a retention of tactile sensation, and he suggests that the different types of anesthesia produced may be sufficient to determine whether the conditions coexist. The only other conditions of practical importance to be considered in the differential diagnosis are: (*a*) An adventitious ligament as reported by Law; (*b*) exostoses of the first rib, which may absolutely simulate cervical rib clinically, as was pointed out first by Mesnard in 1884; (*c*) Raynaud's disease, which Osler[10] divides into mild, moderate and severe types. The mild type, which may never go beyond an acrocyanosis on slight exposure, with sometimes swelling, throbbing and aching in the part affected, the hands more often than the feet may very easily be clinically mistaken for cervical rib, the roentgen ray being necessary for differentiation.

The treatment of cervical rib is divided generally into conservative and surgical Rest in bed for a few weeks with elevation of

[8] Jour. Exper. Med. 1916, **24**, 271, 287.
[9] Monographic Medicine, **4**, 61.
[10] The Principles and Practice of Medicine, 1916, p. 1121.

the arm and sometimes packs, massage, electricity, etc., is to be advised, to cause a subsidence of the acute symptoms, according to Ashhurst;[11] but most writers agree that if the congenital deformity causes any symptoms, conservative treatment is a waste of time, because here one has to deal with a disturbance placed in the way of normal blood and nerve paths which literally assumes the proportion of a foreign body if not removed. All surgeons are agreed in regarding its removal as an exceedingly difficult major operation, and all advise that the periosteum should be removed with the rib to prevent reformation.

The mode of approach varies. Some surgeons advise operation from the front, using either a transverse, oblique or vertical incision. This is the one usually used, dividing platysma and superficial fascia, doubly ligating and dividing the external jugular vein. After dividing the deep fascia and exposing the great vessels and brachial plexus, the vessels and nerves are cautiously retracted from over the cervical rib. The rib is separated from the soft parts, taking care to avoid injury, especially to the pleura, in removing the rib with bone forceps. If complete excision is very difficult, Binnie[12] states that occasionally it may be wise to resect only that portion of bone which is exercising injurious pressure on the vessels or nerves.

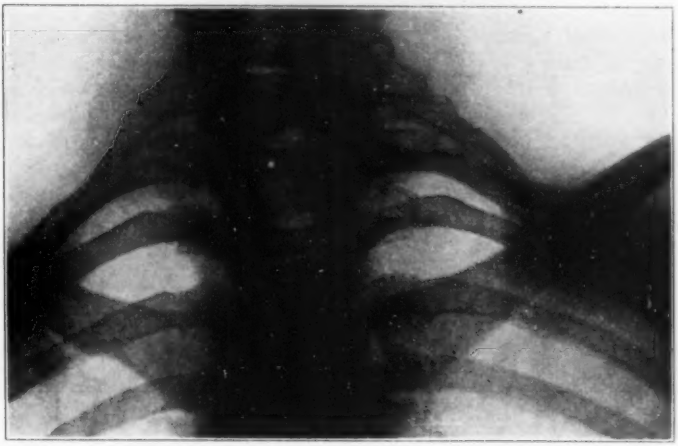
Others advise operation from behind as devised by Streissler and highly recommended by Rovsing[13] recently. A posterior longitudinal incision is made parallel to the spinous processes and about 2 cm. laterally from the midline. The trapezius, both rhomboids, serratus posticus and the splenius, are cut through and the fibers of the complexus and semispinalis are separated. A curved elevator is passed around the neck of the rib and the latter is divided. With this incision, however, the nerve to the serratus as it passes through the scalenus medius is in danger.

Case I.—Female, aged twenty-four years, single, who entered St. Elizabeth's Hospital January 31, 1921, and was discharged, well, seventeen days later. The complaint was "numbness of the whole right arm." Family and past history were essentially negative.

Present Illness. Eight years ago the family physician called her attention to a hump-like prominence at the base of the neck on the right side. Soon after this the patient noticed that she had some numbness of the whole right arm and shoulder, but no other sensory disturbances were noticed. There has been no actual pain or paralysis at any time, although recently there has developed a definite paresis. Patient has had no trouble with her left arm. On physical examination her blood-pressure was found to be essen-

[11] Surgery: Its Principles and Practice, 2d Ed., 1920, p. 582.
[12] Operative Surgery, 1916, p. 209.
[13] Jour. Am. Med. Assn., July 26, 1919, **73**, 376.

tially equal in both arms. The patient was a poorly nourished young woman, physical examination being apparently negative, with the exception of the partial obliteration of both supraclavicular fossæ, the right being practically obliterated. On pressure in the right supraclavicular fossa the patient complained of pain and numbness of the fingers and forearm on that side. The spine showed no scoliosis roentgen ray examination of the cervical spine showed the presence of two short cervical ribs, the right being longer than the left, and both arising from the seventh cervical vertebra. The laboratory report showed the blood and urine to be normal. Blood Wassermann was negative. At operation the right anomalous rib appeared to join the first rib just below the inner portion of the clavicle. It was exposed at this region with considerable difficulty and divided. It was also exposed posterior to the brachial plexus



Case 1

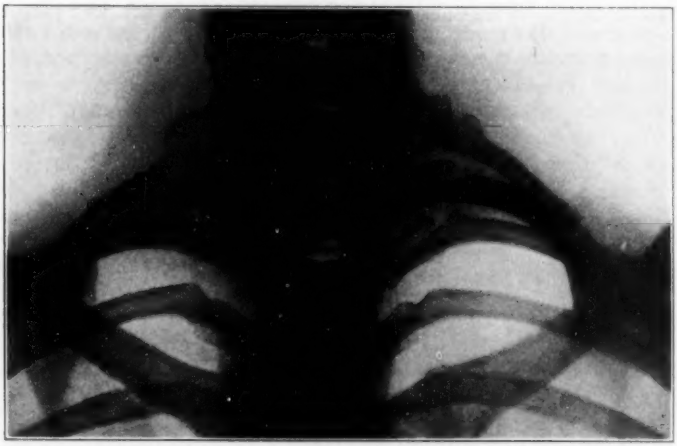
and divided, and the section between these two points was removed. The segment which was removed consisted of a specimen of bone about one and three-eighths inches long, roughly resembling a metacarpal bone. Following this the brachial plexus and the subclavian vessels fell back in what would be their normal position. The wound was closed by suturing the superficial fascia and fat with a continuous suture of No. 00 tanned catgut and closing the skin with a subcuticular suture of silkworm gut.

The patient was placed in such a position that the head inclined toward the right shoulder and was kept in this position for twenty-four hours. Postoperative notes showed the patient had no motor or sensory disturbance and her recovery was uneventful.

Diagnosis. Bilateral cervical rib with pressure symptoms on the right side.

Case II.—Female, aged twenty-one years, single, who entered St. Elizabeth's Hospital March 22, 1921, and was discharged well fifteen days later. The complaint was "blue and cold fingers of the right hand." Family history and past history were essentially negative.

Present Illness. Began about four months ago, when she noticed her forefinger, middle and little fingers turn white and the nails blue whenever she was exposed to cold. No pain at any time. Physical examination showed a hump-like prominence in the right supraclavicular fossa. Over the subclavian artery a distinct thrill and bruit were discovered. The hands and fingers were apparently normal except when one exerted pressure on the right subclavian



Case 2

artery, at which time the fingers became pale and the finger-nails blue. The blood-pressure in both arms was essentially the same. Laboratory report showed the blood and urine to be normal. Blood Wassermann was negative. At operation the rib was exposed and divided with bone forceps, first at its anterior end, and as the distal portion of the rib was firmly attached to the first rib, it was necessary to remove the remainder piecemeal. The specimen consisted of four fragments of bone which measured in total about two and a half inches. The largest fragment was removed from immediately beneath the brachial plexus and subclavian artery. Recovery was uneventful.

Diagnosis. Right cervical rib with pressure symptoms. Exostosis on the left seventh cervical vertebra.

Conclusions. The pressure on the nerves and bloodvessels inducing pain, or even paresis of the arm, makes the subject one of surgical interest.

While the roentgen ray has been the means of confirming many tentative diagnoses of the anomaly, a comparison of clinical and necropsy statistics show that a large number escape detection. This is mainly because, as pointed out by Henderson, about 90 per cent of the cases are symptomless. Fischel in his necropsy findings reports the deformity in 1 per cent of cases, while Henderson states it was clinically recorded in only 31 of 80,000 patients examined at the Mayo Clinic.

The wide range in the variety and degree of symptoms which the patients present makes the diagnosis especially difficult, the one almost pathognomonic sign being a pulsating mass above the clavicle, which Cabot[14] states means cervical rib in nine cases out of ten.

Conservative treatment in some cases has been of value, and apparently even a few cases have been cured by it; but for the reasons stated, whenever signs of compression occur no operation is indicated.

Acknowledgment is made to Dr. J. Shelton Horsley for his permission to report these cases, which occurred on his service.

SKIN TESTS WITH FOREIGN PROTEINS IN VARIOUS CONDITIONS.[1]

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Skin tests with foreign proteins are today being used by numerous investigators and physicians in the study of a large variety of diseases in the hope of identifying a sensitiveness to some foreign protein which may subsequently be shown to be the cause of the symptoms in that patient. This method of diagnosis is being used not only in asthma, hay fever and urticaria, certain cases of which are clearly dependent upon an underlying "asthmatic state," but also in many other conditions in which there is little evidence that hypersensitiveness plays a definite part, but in most of which the symptoms are essentially chronic.

In asthma, hay fever and urticaria, in which so many cases are clearly due to foreign proteins, it is reasonable to suppose for them a

[14] Differential Diagnosis, 1915, p. 338.

[1] From the Anaphylaxis Clinic of the Massachusetts General Hospital.

basis for this sensitiveness which we may call the "asthmatic state," which, in so far as the reactions to the specific protein either by ingestion or injection are immediate and severe, is akin to the experimental anaphylaxis in animals.

The nature of this "asthmatic state" is unknown, but its presence perhaps explains why the symptoms due to foreign protein absorption may result in one patient in urticaria while in another patient they result in chronic headache or chronic indigestion, etc. The present paper is an attempt to review recent literature on this subject and to present the results of my own studies.

In a recent publication[2] an attempt was made to classify cases of asthma and allied conditions. In describing the results of skin tests in asthmatics, attention has been paid to this classification.

Skin tests have been known since 1873. At that time Blackley[3] noted that the installation of crude pollen into the eyes of hay fever patients produced swelling of the mucous membrane. In a later experiment he found that pollen grains when rubbed into a break in the skin produced a local reaction, and he likewise found that a decoction of the pollen could in certain instances produce the same result. Dunbar,[4] in 1903, demonstrated that this local reaction was not due to the mechanical structure of the pollen granules, since it could be obtained by an alcoholic or saline extract of the pollen.

In 1905 von Pirquet and Schick[5] in their classical description of serum disease noted that a reinjection of horse serum causes an intensive edema around the point of injection. Such a development of sensitiveness following artificial sensitization has been shown to occur after an incubation period of seven to ten days and to follow the appearance of the serum disease itself.

In 1912 Schloss[6] described skin tests by the von Pirquet technic to egg-white, and demonstrated that the various chemical fractions of egg-white could each one produce a reaction. He also described skin tests to nuts and to oatmeal.

In 1914 Goodale[7] demonstrated that when a drop of horse serum was placed into a superficial cut in the skin of patients suffering from horse asthma, a local reaction appeared, and also that a drop of the same horse serum placed on the anterior turbinate caused violent sneezing with typical symptoms of horse asthma. A little later he studied hay fever, and found local skin reactions to dilute

[2] Rackemann, F. M.: A Clinical Classification of Asthma. (See Am. Jour. Med. Sci., December, 1921, **162**, 802.)

[3] Experimental Researches on the Cause and Nature of Hay Fever, London, 1873.

[4] Hay Fever, Journal of Hygiene, 1903, **13**, 105.

[5] Die Serumkrankheit, Leipzig, 1905.

[6] A Case of Allergy to Common Foods, Am. Jour. Dis. Children, 1912, **14**, 341.

[7] Skin Reactions in Anaphylaxis, British Med. and Surg. Jour., 1914, **171**, 695.

alcoholic extracts of those plant pollens which corresponded accurately to the dates of onset and subsidence of the hay fever. Talbot,[8] in 1914, studied infants by testing their skin with egg-white and found that in all cases in which egg caused indigestion there was a violent skin test to the protein.

In recent years the literature has remarkably increased to its present considerable size. Positive skin tests do not occur in normal individuals, and when they do occur in those who are apparently normal, there is always a reason, although in many cases no satisfactory explanation can be given. Schloss[9] has recently shown that a positive skin test indicates that the patient is sensitive to that protein, but there are undoubtedly differences in the behavior of adults and children in this respect. In 1916 Talbot[10] performed skin tests with egg-white as a routine on every admission to his ward and found 3 positives out of 85 tests. No further studies in the 3 were made. Throughout the literature are many notes of positive tests in adults for which there is no explanation. In the present study, skin tests with a variety of at least 15 different proteins were done with negative results in a total of over 600 patients, in most of whom sensitiveness to proteins was a reasonable and probable explanation of the symptoms. The results of skin tests performed by other observers are rather difficult of analysis chiefly because of the fact that the proteins used are differently prepared and that the methods of application are also different.

Walker has probably done as much in this field as anyone. In 1918 his study of 400 patients with asthma[11] showed that 48 per cent gave positive tests, but of the 130 patients below the age of twenty-five years, 64.5 per cent were positive and of those below the age of fifteen years, 69.1 per cent were positive. These tests were made by the same technic as the writer's.

A large series of 800 tests has recently been reported from the Mayo Clinic by Sanford,[12] who, using Walker's technic, found over 25 per cent of the cases positive; no attempt at grouping these patients was made.

Gottlieb[13] did skin tests with a large number of test substances in 32 patients, finding one or more positive results in 23. Sterling[14] found only 1 positive in a series of 12 asthmatics tested. Skin tests in dermatology have been recently shown to be of some import-

[8] Asthma in Children, Boston Med. and Surg. Jour., 1914, **171**, 708.

[9] Loc. cit.

[10] Asthma in Children, II, Boston Med. and Surg. Jour., 1916, **175**, 191.

[11] Walker, I. C.: Clinical Study of 400 Patients with Bronchial Asthma, Boston Med. and Surg. Jour., 1918, **179**, 288.

[12] Protein Sensitization in Asthma and Hay Fever, Jour. Am. Med. Assn., 1920, **74**, 124.

[13] Results of Tests in Hay Fever and Asthma, Jour. Am. Med. Assn., 1920, **75**, 814.

[14] Results of Tests for Food Protein Sensitiveness in Small Group of Asthmatics, Pennsylvania Med. Jour., 1918, **22**, 135.

ance. In 1916 Strickler and Goldberg,[15] using purified alkaline salt solution extracts of various foodstuffs, found 11 positive reactions in testing 29 cases of various dermatoses. Their work, however, has been supplanted by the careful studies of Schloss,[16] whose results are as follows: Urticaria, angioneurotic edema and erythema multiforme, 19 positives in 72 patients (26.3 per cent); eczema under sixteen months, 53 cases with 40 cases (77.4 per cent) giving positive reactions; eczema over sixteen months, 24 cases with 10 positive tests (41.6 per cent). O'Keefe[17] studied the skin tests in 70 cases of infantile eczema and found that 29, or 41 per cent of these patients, gave a positive reaction to one or more foods, egg-white being the commonest offender.

While, then, positive tests are always important, negative tests are by no means of equal importance, as has been recently brought out by Schloss,[18] who has observed that in a sensitive individual cutaneous tests may become negative because of a temporary desensitization.

The cases reported in the present work are only those in whom a relatively large number of tests have been done, so that in the case, for example, of hay fever the number appears small. There are two methods of testing the skin: (1) The cutaneous method, by which a small quantity of dry protein powder is mixed *in situ* on the arm with a diluent and a scratch made through the resulting solution; positive reactions appear within fifteen to twenty minutes and last for about two hours. (2) The intradermal method by which a measured quantity of sterile protein solution in known concentration is injected between the layers of the skin. Tests by the intradermal method appear within five to fifteen minutes and disappear in about one hour. They are very delicate and in the author's hand have been found accurate and easy of interpretation. Indeed, in several cases in which it was of the utmost importance to determine accurately whether certain seasonal symptoms were due to hay fever or not, the cutaneous (scratch) tests to ragweed and timothy pollen in a strong (1 to 100) dilution were negative, whereas the intradermal method using these two pollens in a weaker (1 to 1000) dilution demonstrated a definite sensitiveness to pollen.

On this point Walker[19] concludes, after some study, that the intradermal is less specific and is too sensitive. There is, of course, no question that the intradermal method is more difficult of application, since in the first place a chemically as well as a bacteriologically clean syringe and needle are required for each test, and in

[15] Anaphylactic Food Reactions in Dermatology, Jour. Am. Med. Assn., 1916, **66**, 249.

[16] Allergy in Infants and Children, Am. Jour. Dis. Children, 1920, **19**, 433.

[17] Dietetic Infantile Eczema, Boston Med. and Surg. Jour., 1920, **183**, 569.

[18] Loc. cit.

[19] Comparison between Cutaneous and Intradermal Skin Tests, Jour. Med. Research, 1917, **37**, 287.

the second place the proteins used must be in a sterile solution which produces absolutely no reaction when injected into normal persons. This method is delicate. In the interpretation of any of these tests it is important not to read as positive, reactions above any certain size, but rather to read the test according to their relative sizes and to compare them directly one with another and with the control test. The typical positive test by either method should consist of an urticarial wheal having a sharply defined irregular border; it is usually pale in color but is surrounded by a zone of bright erythema. All tests by all methods should give entirely negative reactions in normal individuals.

The present study is based upon skin tests done by the cutaneous method, using the proteins in some of the common foods as well as in the animal dusts and danders.[29] Only those cases are reported in which at least fifteen different test substances were used, though in most of the cases from twenty to thirty tests were employed.

The list of test substances includes:

Wheat proteose	Horse-hair	Casein	Timothy
Wheat leucosin	Cat-hair	Cow's milk	Bean
Buckwheat	Dog-hair	Beef	Pea
Rye	Goose feathers	Pork	Lima beans
Barley	Chicken feathers	Chicken	Potato
Oat	Sheep wool	Lamb	Peanut
Rice	Egg-white	Codfish	Strawberry
Corn	Egg-yolk	Mackerel	Wheat globulin
Horse dander	Lactalbumen	Ragweed	Wheat.
Orris powder			

In certain cases, and in addition to the cutaneous tests, the intradermal method with solutions of the pollens, of egg-white or of horse-hair extract was used for corroboration in case a corresponding sensitiveness was expected from the history.

Hay Fever and Pollen Asthma. When the symptoms of hay fever occur only during the pollen season, tests to foods, etc., are not ordinarily indicated. Such tests were done in 118 cases, all of which had, of course, a positive test to one or more pollens and in most of which the history vaguely suggested a possible susceptibility to foods, horses, etc. It was found that in 48 instances, or about 40 per cent of these patients, there was a positive test to some protein other than the pollens.

TESTS IN HAY FEVER SHOWING THE NUMBER OF CASES IN WHICH TESTS TO FOODS, DUSTS, ETC., WERE POSITIVE.

	Total tests.	Number positive.	Per cent positive.
Late hay fever	24	11	45.8
Early hay fever	19	5	26.3
Double hay fever	16	9	56.2
Pollen asthma	37	14	38
Complicated pollen asthma	22	9	41
	118	48	40.6

[29] The proteins used were obtained from the Arlington Chemical Company.

It is noteworthy that the proportion of other positive tests was greater in adults than in children with pollen sensitiveness.

If we analyze these positive cases we find that in the adults the cereals gave positive tests in 16 cases, and in each case the food was withdrawn from the diet, but in none of these cases can it be said that this withdrawal produced any good result; and in none of the cases was the patient aware of the sensitiveness before the tests were made.

Animal dusts gave positive tests in 11 adults, and here the story is different because in 6 of these patients withdrawal of feather pillows consequent upon the positive test to goose feathers, brought about a definite improvement in the symptoms. In 2 adults positive tests were obtained to each protein in the dust group, namely: horse, cat, dog and feathers, but only 1 patient (R. J.) knew that she could not go near cats without trouble.

In children with hay fever there were only 6 cases in which a positive test to foods was obtained, although such tests were performed in 21 cases of the 51 children suffering from pollen sensitiveness.

Horse Asthma. There were 45 cases of horse asthma of all ages—a diagnosis made only in case the positive test to horse dander or to horse-hair extract[21] or to both was substantiated by the patient's knowledge of susceptibility to horses or by the fact that his asthma was associated with certain places in which animals were in evidence. In 15 cases of horse asthma, tests with other proteins showed positive results as follows: Wheat proteose in 1 case, wheat leucosin in 2 cases, cat-hair in 5, dog-hair in 4, goose feathers in 3 and ragweed, timothy and pea in 2 each, and egg-white, egg-yolk and beef in 1 each. Avoidance of the corresponding proteins was advised in each case.

Dust Asthma. In addition to cases of horse asthma there is a group of 31 patients with "dust asthma" in which group is included those cases with sensitiveness not only to animal dusts as feathers, cat and dog hair, but also to other substances existing in dust, as wheat flour, orris powder, etc. This subgroup of asthma is so complicated and at the same time so important that it has seemed best to tabulate the results as found in the 17 adults and 1 child. (See Chart I.) Thirteen patients are not tabulated since only a very few tests were done and yet the asthma in each was definitely associated with some particular occupation or environment: a coffee worker gave a very fair test to coffee dust.

A study of Chart I shows that 6 adults and 1 child were sensitive to feathers, a fact corroborated by the relief to their asthma following the removal of feather-pillows. But although each patient is sensitive to feathers, yet there are many other positive

[21] These two terms "Horse Dander" and "Horse Hair Extract" refer to two different preparations used in the tests.

CHART I. DUST ASTHMA. ADULTS AND CHILDREN. 18 CASES. SKIN TESTS TO FOREIGN PROTEINS IN.

Number.	Initials.	Age.	Family history.	Wheat protoose.	Wheat Leucosin.	Buckwheat.	Rye.	Barley.	Oat.	Rice.	Corn.	Horse dander.	Horse-hair.	Cat hair.	Dog hair.	Goose feathers.	Chicken feathers.	Sheep wool.	Egg white.	Egg yolk.	Lactalbumen.	Casein.	Cow's milk.	Beef.	Pork.	Chicken.	Lamb.	Codfish.	Mackerel.	Ragweed.	Timothy.	Beet.	Bean.	Pea.	Lima bean.	Potato.	Peanut.	Wheat globulin.	Wheat.
	Feathers																																							
1	SMG	12		X	X											X																							
2	JJS	35		X	X											X																							
3	KG	39		X	X											X																							
4	WE	32		X	X				X							X																							
5	HB	22		X	X				X			X				X																							
6	IW	37		X	X				X			X				X																							
7	ADP	19		X	X				X			X				X																							
	Wheat																																						
8	AP	58		X	X		X	X	X																														
9	MM	38		X	X		X	X	X																														
10	WL	16		X	X		X	X	X																														
11	AK	40		X	X		X	X	X																														
12	MB	26		X	X		X	X	X																														
13	FA																																						
	Unknown																																						
14	CH	27	X									X																											
15	WR	26	O									O																											
16	KN	34																																					
17	SC	30		X	X	X	X	X	X	X																													
18	LW	21		X	X																																		

tests. Indeed, all but one of these patients react to at least three other proteins besides feathers. In Cases 3 and 4 with definite sensitiveness to wheat, bread and cereals were also removed from the diet, but were subsequently added again without increasing the symptoms. Eight patients, including 2 not charted, were sensitive to the wheat proteins and each gave a history of asthma aggravated by contact with flour dust such as in making bread. Five of these 8 were professional bakers, the other 3 being housewives. In this wheat group there were positive tests not only to other cereals but to odd proteins, such as pea, potato and lamb, the significance of which is unknown.

This sensitiveness to a number of different proteins—multiple sensitiveness—may be particularly marked, a fact which often adds to the difficulty of correct diagnosis. For example, the findings in 5 other patients are added to Chart I. In these 5 patients asthma was worse under certain fairly definite circumstances not adequately explained by the positive tests obtained.

Thus it is apparent that the finding of a positive test does not always explain the actual cause of symptoms. In other words, to be conclusive, positive tests must be confirmed by the patient's history or must be controlled by subsequent clinical experiments. It is, of course, self-evident that thoroughly complete tests would be almost impossible of performance because of the unlimited number of possibilities, so that the causative proteins might easily have been overlooked.

Food Asthma. In only 19, or 3 per cent, of the 648 cases of asthma were proteins in food considered to be the cause of symptoms. As in the case of dust asthma, so here positive tests were invariably found to be multiple and in most cases not confined to one protein group. With the help of the history as well as by clinical experiment it was determined that the asthma in these cases was due in 10 cases to egg, in 4 to wheat, in 2 to meat and in 1 each to nuts, fish and milk. In 4 others the positive tests were so numerous and complicated that no one food could be held responsible.

Bacterial Asthma. In the present series a diagnosis of bacterial asthma (including perennial asthma) was made in 156 patients, and of these about 100 had fairly complete skin tests. Out of 103 patients tested 22 showed positive reactions. An analysis of the results obtained in these cases shows that positive tests to only one protein were obtained in only 3 cases, while 1 other patient had only two positive tests. Two other patients had a number of different positive tests but all to substances in one protein group. The diagnosis of bacterial asthma was made in these last 2 cases largely by exclusion, as it was subsequently established that avoidance of the particular group of proteins did not bring relief to the symptoms. In other cases positive tests were scattered throughout the protein groups. One of these cases of bacterial asthma gave beautiful tests

to the wheat proteins and to barley, rye and oats; but when it was discovered that he was a diabetic, and in recent years had rarely if ever eaten wheat or cereals of any sort, and when all chances of his exposure to cereals and grain dust had been excluded, the absurdity of the test finding in this particular case was evident.

Emphysema. In the cases of emphysema skin tests were done in 133 cases, but in only 34 were positive results obtained. This latter figure includes 13 cases of emphysema on a background of pollen asthma and 8 cases on a background of animal dust asthma. Here, again, positive results were found to be well distributed throughout the various protein groups and were confined to one group in only 3 cases. Except for the 21 cases whose emphysema could be shown by history, skin tests and reaction to treatment to be due to foreign proteins, no one of the other 13 patients with positive tests gave any history of sensitiveness to proteins.

Six of these 13 patients were found to be sensitive to one or more of the cereal proteins, and were told to avoid all bread and cereals, but it is difficult to know how much this advice has helped them, especially as in certain cases they have, after a trial of from three weeks to six months, gone back to bread without change in their asthma or emphysema. In a previous publication[22] the relation of emphysema to other forms of asthma was discussed, and in consequence of the findings there it is evident that in the presence of organic changes in the lungs, little in the way of protein treatment can be accomplished.

In this series, skin tests were done in 78 cases of reflex asthma and in 35 cases of "unclassified asthma," but in only 7 of these 113 cases were the results positive.

Other Conditions Allied to Asthma and Hay Fever. In addition to the work on asthma, many patients with other conditions have been tested. Chief among these conditions is vasomotor rhinitis, in which the physical findings in the nose are quite the same as those during the acute hay fever attack. As here used the term refers to a perennial condition which runs on from day to day and from week to week regardless of the environment or occupation of the patient and without any apparent cause for its changes in severity. The cases already described under hay fever, horse asthma and dust asthma are not included.

One hundred and ninety-eight patients with this ailment were tested and studied in some detail. Forty-five, or 22.7 per cent, were found to give positive skin tests. These positive skin tests were confined to one group of proteins in about half of the cases. Although only a few of these patients were heard from after the tests were done, these few were practically all much relieved by the advice to avoid the protein giving the test. Thirteen were sensitive to

[22] Rackemann, F. M.: A Clinical Classification of Asthma. (See AM. JOUR. MED. SCI., December, 1921, **162,** 802.)

orris powder and here the advice to give up its use was often striking. In several cases, the importance of further study is well illustrated: For example: M. G. was a patient whose tests by the cutaneous method were entirely negative and who had been treated with ten doses of a vaccine made from her nasal secretion without result. Finally, the intradermal method revealed a slightly positive test to horse-hair extract, and treatment with this has to date caused a definite improvement.

Five patients were advised to give up their feather pillows, with the result that their symptoms were very much relieved.

Five patients in whom the results were not good, all gave reactions to one or more of the cereal group, but whether their attention to instructions was perfect or not the fact remains that the advice to avoid bread and all wheat was not followed by any definite clinical improvement. The same general experience is true of the other patients with vasomotor rhinitis who gave positive tests in more than one protein group. The large majority of these tests were in the animal hair group, but avoidance of feather pillows was not of any striking benefit. Unfortunately in none of these other patients was treatment with horse-hair carried out. On the other hand 2 of these patients were sensitive to ragweed, and treatment with ragweed extract during the summer seemed to have a definite and permanent good effect upon their condition in spite of the perennial character.

From the above it is perhaps reasonable to conclude that in vasomotor rhinitis the responsible proteins act largely through the respiratory system and that the pure food proteins investigated have little if any effect upon the disease in spite of the fact that they may give a positive skin test. If correct this observation would strongly suggest the possibility of a local tissue hypersusceptibility. In none of these cases did the ingestion of bread or other food protein giving a positive skin test cause any local symptoms in the mouth or stomach, so that, clinically at least, there was no evidence of a local sensitiveness in any other tissue.

In a recent paper on "Frequent Causes and the Treatment of Perennial Hay Fever," Walker[23] found the symptoms were due in 20 cases to emanation from horses, in 6 cases to cats and in a number to feathers. He speaks of similar symptoms among laboratory workers which were due to rabbit and guinea-pig hair, likewise of symptoms in bakers and housewives due to the cereal flours. Unfortunately he does not give the total number of cases studied, but since the numbers as given are small and his clinic is very large, it may be assumed that these proteins are at least infrequent as causes of perennial vasomotor rhinitis, and in so far do Walker's findings agree with my own.

[23] Frequent Causes and the Treatment of Perennial Hay Fever, Jour. Am. Med. Assn., 1920, **75**, 782.

Eczema, Urticaria and Angioneurotic Edema. Forty cases of eczema were studied, 19 in children and 21 in adults. Four adults gave positive tests—3 to orris powder and 1 to egg. In no case was the finding of any clinical importance. The egg case had known of the susceptibility for many years and the eczema had persisted in spite of prolonged egg-free diet. Of the 19 children tested there were 8 cases which gave positive tests (42 per cent)—figures comparable to those of Schloss and of O'Keefe. Each one of these positively reacting children gave a positive reaction to egg-white and 4 of them gave a well-marked test to a large number of wheat proteins in addition. One child gave a test to beef, bean and pea. In no case was a single protein group involved.

The findings of these tests, with the consequent elimination of egg from the diet, brought about excellent clinical results in 4 of these 8 children, but in another patient elimination of egg had been carried out for some months before the tests were done and without any appreciable benefit to the eczema.

Urticaria. Out of a total of 35 cases tested, only 4 adults and 2 children gave positive results. Avoidance of the protein did not relieve the adults at all but, as in eczema, 1 of the children reacted among other things to egg, while the other reacted to wheat, buckwheat and bean, and both were improved when the corresponding foods were omitted from their diet.

Seven cases of angioneurotic edema were tested, and 2 patients gave positive tests. Both were in women who reacted to wheat as well as to one of the animal dusts, but unfortunately neither was seen again.

Miscellaneous. In addition to the cases noted above, in many of which protein sensitiveness is a very reasonable working basis, tests were also made in a number of other conditions not so closely related to this clinical group. These cases, 86 in number, included 19 cases of frequent colds in children, 2 of whom gave positive tests, 1 to ragweed pollen compatible with her hay fever, the other to feathers; 4 adults with chronic winter coughs were tested, 1 of whom was found positive to wheat, which finding was clinically unexplained; 6 cases with obscure chronic arthritis were tested with no positive results; 4 cases of cardiospasm were studied as completely as possible, but no positive results were obtained; 8 cases of chronic skin disease, including 3 of psoriasis, were all negative. Eighteen normal individuals were, of course, negative.

Twenty-seven patients with other conditions, including such as paroxysmal tachycardia, periodic vomiting in children, chronic headache, herpes labialis, recurrent conjunctivitis, etc., were tested with only one positive reaction in a patient, who also had late hay fever. Thus in this total group of 86 cases there were only 4 cases with positive tests, in 2 of which the tests were a mere observation without reasonable explanation.

Summary. In this work skin tests in 939 patients presenting various clinical conditions have been studied. It is to be expected that positive skin tests should occur together in the same protein group; that a patient with horse asthma should give a skin test to cat- or to dog-hair as well as to horse dander. Multiple tests are commonly obtained with several of the proteins in any one group, but they are also obtained to proteins in other groups. That there is no one test substance in any one group which can be used in a given case to be quite sure of ruling the entire group in or out is shown by such observations as that in the cereal group (see Chart I); many patients react to wheat proteose, but 3 adults fail to react to it, while in the animal group horse-hair and horse dander give by far the greater number of positive tests; but 2 children and 1 adult react to goose feathers and fail to react to horse at all. Thus in any given case a wide variety of tests should be done. A more perfect method of excluding proteins is to so limit the patient's diet and life that, as far as possible, contact with proteins is limited to those represented by the negative tests found.

Chart II represents a summary of the results in the various clinical conditions mentioned. It is interesting to add the tests together and then determine the relative incidence of positive results with each test substance. Chart III shows such an addition, compiled from only those cases accurately tabulated.

CHART II.—RESULTS OF SKIN TESTS IN THOSE PATIENTS TESTED WITH FIFTEEN OR MORE DIFFERENT SUBSTANCES.

Diagnosis.	Patients, total	Patients tested	Patients positive	Positive per cent
Hay fever (simple)	347	59	25	42
Pollen asthma	136	59	23	39.0
Horse asthma	45	45	15	33.3
Dust asthma	31	31	31	100.0
Food asthma	19	19	19	100.0
Bacterial asthma	156	103	22	21.0
Emphysema	136	133	34	25.0
Reflex	78	78	4	5.0
Unclassified	47	35	3	8.5
Total asthma	648	503	151	30.0
Vasomotor rhinitis	198	198	45	22.7
Eczema	40	40	12	30.0
Urticaria	35	35	6	17.0
Angioneurotic edema	7	7	2	28.5
Total allied conditions	280	280	65	23.0
Miscellaneous	86	86	4	4.6
Grand total	1361	928	245	26.4

Figures refer to positive tests with substances other than the one to which the patient gave a history of sensitiveness.

CHART III.—NUMERICAL INCIDENCE OF POSITIVE RESULTS WITH EACH INDIVIDUAL TEST SUBSTANCE AS OBTAINED IN THOSE PATIENTS IN WHOM AT LEAST TEN SEPARATE TESTS WERE DONE.

Diagnosis.	Number of patients tested.	Wheat proteose.*	Wheat leucosin.*	Wheat globulin.	Whole wheat.	Buckwheat.†	Rye.*	Barley.*	Oat.*	Rice.†	Corn.	Horse dander.*	Horse-hair.	Cat-hair.*	Dog-hair.*	Goose feathers.*	Chicken feathers.†	Sheep wool.	Egg-white.*	Egg-yolk.	Lactalbumen.*	Casein.	Cow's milk.	Beef.†	Pork.	Chicken.	Lamb.	Codfish.*	Mackerel.†	Ragweed.*	Timothy.*	Beet.†	Bean.*	Pea.†	Lima bean.†	Potato.
		939	939	160	304	568	783	786	939	426	278	939	134	792	778	919	312	115	939	248	939	74	86	246	94	116	225	876	683	750	750	422	805	643	572	326
Total hay fever and pollen asthma		11	7	1	1	3	3	8	4	1	1	9	4	4	3	8	1	..	1	..	2	....		.....				1	1	26	9	2	4	1	3	3
Dust asthma		8	8	2	4	2	7	5	7	1	..	4	2	2	4	9	4	..	.....					.....	1			1	..	3	..	1	1	4	..	1
Food asthma		5	6	..	3	3	1	1	4	1	1	3	2	1	..	1	1	..	9	2	4	....		1	..	3	1	1	..	1	..	3	1	..	2	
Horse asthma		1	2	....	1	.....					1	13	15	5	2	2	1	..	1	1	.....			.....						2	2	..	2			
Bacterial asthma		4	6	2	1	..	1	1	2	....		1	3	1	1	2	2	2	3	.....				.....						4	1	..	2	..	1	
Reflex asthma		..	2	....	1	1	.....					..	..	2	1	1	....		.....					.....						2	..	.....				1
Perennial asthma		1	1	.....	1	.....						..	..	3	1	2	....		....	1	....			1	.....					2						
Emphysema		6	3	....	1	3	2	.....				4	5	2	3	5	2	..	1	..	1	....		1	.....					6	..	1	1	1	..	1
Eczema		4	3	..	1	3	2	2	1	1	1	..	1	....	1	..	2		6	3	1	....		1	.....					1	1	2	1			
Vasomotor rhinitis		7	12	4	3	3	4	4	1	1	..	4	5	3	4	6	5	..	1	..	2	....		..	1	.....				4	..	1	..	1		
Urticaria		2	1	....	1	..	1	2	2	..		..	.....					1	4	1	1	....		.....						2	2	..	1	..	2	
Angioneurotic edema		..	1	.....								..	1	1	..	1			.....					.....						1						
Miscellaneous		1	1	.....								..	.....			1	....		.....					.....												

Substances marked * were used almost as a routine in the 939 patients tested.
Substances marked † were used in over half of this number.

Discussion of the Value of Skin Tests in General. In such conditions as hay fever, horse asthma and perhaps dust asthma, when the history shows a fairly definite and obvious relation of symptoms to some one protein, the skin test, of course, demonstrates this protein etiology. In certain doubtful cases with a suggestive history the test is of greatest value in determining whether or not the proteins suggested by that history are important or not in the etiology.

Aside from its use in diagnosis the skin test is of use in the treatment of such conditions as hay fever in order to determine the dilution of pollen extract to use at the start.

Skin tests probably demonstrate a sensitiveness to proteins in all cases in which they are positive, but it is well known that many tests are found in the clinic for which there is little if any explanation. Clinically, at least, positive tests should be taken seriously only in case they are compatible with the patient's history or in case further study and clinical experiment can prove their importance as an etiological factor.

In cases of asthma which are, at first glance, evidently dependent upon bacterial infection the skin test may often reveal a protein sensitiveness which may prove to be the fundamental starting-point of the symptoms. This is particularly true in cases of asthma which occur in the autumn and in which a test to ragweed extract is found. Such cases can best be treated by prevention the following year. In a certain relatively small number of cases, especially in children, the tests are of greatest value in demonstrating the cause of symptoms, and in most of these cases treatment by avoiding the corresponding food gives remarkable results.

In the present series there are approximately 100 cases in which positive tests of a fairly definite sort were obtained which were evidently not compatible with the history. Subsequent study showed, moreover, that in only about 13 of these cases was the finding of the test to food or animal protein really important and of use in further treatment. This figure is very small, but, as a matter of fact, the ability to really help a small number of patients undoubtedly justifies the great amount of routine work on many other patients. Emphasis should be placed upon the necessity of a fairly gross interpretation of any positive test. Too delicate or fine a reading merely clouds the picture and in addition renders further progress in this already obscure branch of science even more difficult.

ENZYME MOBILIZATION BY MEANS OF ROENTGENRAY STIMULATION.

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It is at present a recognized principle in the therapeutic application of photodynamic and radiant agents, including roentgen rays, radium, Finsen and red rays, sunlight, etc., that, apart from the direct effect on the exposed tissue, these agents may bring about a distinct systemic alteration.

Clinically this alteration is made evident in two ways: There is first of all the recognition that the effects of radiant agents may be exerted on remote pathological lesions. Thus lupus and other tuberculous processes may be benefited by light rays acting on remote body surfaces. Secondly, we recognize a general intoxication, a phenomenon of varying intensity, ranging from mere transitory and subjective symptoms to an actual fatal intoxication. To these latter forms the term roentgenray anaphylaxis has not infrequently been applied, but, of course, improperly. The general intoxication is frequently elicited when large lymphatic structures, abdominal viscera or cell-rich neoplasms or inflammatory exudates are exposed for any length of time. Walsh[1] is said to have been one of the first observers to record such toxic effects.

The mechanism of this reaction, apart from the assumption that it is due to the reabsorption of the products of cell destruction, has not been clearly defined. It is known that the intracellular enzymes are influenced by the agents under consideration, and experiments to study the effects upon ferments *in vitro* have demonstrated the destructive effect of radiant energy upon them, the diastasic ferment being the only one that displays considerable resistance to prolonged exposure.

Short exposures, on the other hand, may accelerate enzyme action *in vitro*, according to Richards.[2]

If the possibility exists that by means of irradiation the intracellular enzymes may be altered and their entrance into the blood and lymph current accelerated or retarded, it might seem a plausible method of approach to the problem of altering and controlling the amount and character of the serum ferments and the

[1] British Med. Jour., 1897, **2**, 272.
[2] Am. Jour. Physiol., 1914, **35**, 224.

resultant effect on such local pathological processes as pneumonia[3] and tuberculosis.[4]

We cannot introduce foreign ferments directly into the circulation because of the impossibility of freeing them from more or less toxic admixtures; the advocacy of trypsin injections by Beard,[5] it will be recalled, was along this line but led invariably to a toxic reaction. The intestinal absorption of enzymes is likewise uncertain. The ferment-rich abdominal organs might, however, lend themselves to stimulation by means of the agents under consideration, and, as a result of varying degrees of insult, discharge ferments into the circulation in different amounts. Whipple[6] has noted that liver injury, for instance, causes an increase in the serolipase, and Musser and Edsall,[7] in studying the effect of roentgen rays on the metabolism of leukemic patients surmised that an acceleration of the proteolytic activity resulted from the roentgenray treatment. It may be permissible to quote at length from their interesting paper: "The facts that have just been mentioned demonstrated, we think, that the effect (of the roentgenrays) is not a direct one but one that requires response on the part of the individual. . . . To be more specific concerning the processes that are stimulated and accelerated by the roentgen rays, we consider that it is highly probable that the action is chiefly on autolysis. A considerable number of physiological and pathologic processes have, with considerable probability, been shown to be due to autolysis, that is, to activities that have the characteristics of ferment-like processes and that produce in their course the same classes of substances as those found in the various stages of digestion. The view is now widely accepted that the exudate in pneumonia undergoes resolution as a result of sudden autodigestion, carried out not through bacterial influences but through the activities of the tissues. . . . Following the general trend of the thought, and the direction in which the results of recent experimental work pretty generally point, the most natural explanation of the increase in tissue destruction, when this destruction is dependent upon individual body reaction, is that it is due to acceleration of autodigestive or autolytic processes. The remarkable suddenness and intensity with which the action of the roentgen rays begins immediately after exposure is more direct evidence in favor of the view that autolysis is influenced."

In a second contribution (Edsall and Pemberton[8]) the effect of roentgen rays on unresolved pneumonia was studied as well as

[3] Jobling, J. W., Petersen, W. F., and Eggstein, A. A.: Jour. Exp. Med., 1915, **22**, 568.

[4] Petersen, W. F.: Arch. Int. Med., 1918, **21**, 14.

[5] Enzyme Treatment of Cancer, London, 1911.

[6] Bull. Johns Hopkins Hosp., 1913, **24**, 357.

[7] Tr. Assn. Am. Phys., 1905, **20**, 294.

[8] Am. Jour. Med. Sci., 1907, pp. 133, 286 and 426. Tr. Assn. Am. Phys., 1906, **21**, 618.

attention directed to possible toxic results that might be related to the effects of the roentgen rays. In these two papers the very definite foundation for the therapeutic application of the rays in stimulation enzyme activity, thereby influencing pathologic processes, was formulated.

Since these papers of Edsall were published a considerable amount of evidence has been accumulating that tends to confirm the view that apart from the antibacterial mechanism involved in recovery from pneumonia a second mechanism, the inception of an active autolysis, plays a considerable role in the crisis (Jobling, Petersen and Eggstein,[9] Lord,[10] Weiss,[11] Blake and Cecil,[12] Petersen and Short,[13] Thomas and Parker,[14] etc.).

In the meantime there has developed, first quite empirically, the so-called non-specific method of treatment of a number of diseases whereby disease processes are either abruptly terminated or markedly influenced by the intravenous injection of a great number of different agents ranging from chemicals—salts, formalin, etc.—through the metallic colloids—silver, arsenic, etc.—to various biological substances—vaccines, milk, protein split products, etc. The intensive study which interest in this field has stimulated, has led to the recognition that the broad basis of this form of therapy rests on common systemic alterations produced by these various substances. Weichardt[15] uses the general term "plasma-activation" to cover the whole series of alterations inaugurated by the non-specific injections. Among these the alteration in the permeability of the cells is perhaps fundamental. The serum enzymes, too, have been found altered, particularly the proteolytic enzymes are seemingly increased in amount. Lindig,[16] Luithlen[17] and others regard this mobilization as of particular significance. Sachs,[18] in his recent review, seems to be of the same opinion.

Considering the fact that the enzyme mechanism very probably plays a role in such pathological conditions as pneumonia and tuberculous infection, and that even in the non-specific reaction the effect of enzyme mobilization is supposed to be of some importance, we thought it might be of interest to study whether by means of the roentgen ray or other similar agents we could bring about the "shedding" of organ enzymes. Studies heretofore reported, such as those of Hall and Whipple,[19] are concerned chiefly with the cause of the roentgen ray shock when large doses are used, while Denis, Martin and Aldrich[20] endeavored to elucidate the same point

[9] Exp. Med., 1915, **22,** 568.
[10] Jour. Am. Med. Assn., 1919, **73,** 1420.
[11] Arch. Int. Med., 1919, **23,** 395.
[12] Jour. Exp. Med., 1920, **31,** 445.
[13] Jour. Infect. Dis., 1918, **22,** 147.
[14] Arch. Int. Med., 1920, **26,** 125.
[15] München. med. Wchnschr., 1918, **65,** 581.
[16] Ibid., 1919, **66,** No. 33.
[17] Wien. klin. Wchnschr., 1913, **26,** 653.
[18] Therap. Halbmonatschr., 1920, **34,** 379.
[19] Am. Jour. Med. Sci., 1919, **157,** 453.
[20] Ibid., 1920, **160,** 555.

by means of massive regional doses in rabbits. Pfeiffer,[21] on the other hand, has already demonstrated that in photodynamic intoxication (he used "rose bengale") a mobilization of serum peptidase takes place.

Apart from the mobilization of enzymes the selective stimulation of organs by means of the roentgen ray or related agents is a related field in which therapeutic applications have been reported only in very recent papers. These include the alteration in the coagulation mechanism following raying of the spleen (Stephan[22]) and the effort to increase the function of certain of the glands of internal secretion by means of stimulating doses.

Experimental. Preliminary experiments were carried out to determine whether variation in enzyme titers occurred in the serum following roentgen ray exposure of the liver, intestinal and splenic area.

Liver Exposure. Dog of 14 kilo. Diet, June 13 to 29, 1917, as follows:

Protein (lean meat)	220 gm.
Carbohydrate (cracker meal)	60 "
Fat (lard)	40 "
Bone ash	35 "
Water	300 "

From June 29 to the termination of the experiment the daily ration was altered so that the animal received 100 gm. of carbohydrate and 25 gm. of fat per day. The normal metabolism of this diet was first studied for a period of several days.

On June 20 (10 A.M.) the liver area was rayed for fifteen minutes (Coolidge tube, 10-inch distance, 8 ma. and 5-inch back spark; no screen). On June 25 the liver was exposed for thirty minutes (8-inch spark) and on June 29 for one hour. (In raying the liver area, parts of the gastro-intestinal tract, pancreas, etc., were, of course, not to be excluded). After a period of four days a superficial burn followed over the area exposed. The animal was killed on July 5. No gross or microscopic alterations were to be found in the abdominal viscera.

It was observed that:

(*a*) The weight of the animal decreased after the second exposure. (about 1000 gm.)

(*b*) That the nitrogen excretion also increased after this exposure. The serum studies revealed the following changes:

(*c*) Exposure was followed by a transient decrease in the non-coagulable nitrogen of the serum with an increase in the amount later. From the original of about 40 mg. per 100 cc the non-coagulable nitrogen increased to 55 mg. at the end of the experiment.

[21] Ztschr. f. Immunitätsforsch., orig., 1915, **23**, 597.
[22] München. med. Wchnschr., 1920, **67**, 309.

(*d*) A marked mobilization of the protease followed the short exposure and there was no change following the two longer periods of exposure to the rays.

(*e*) The ereptase (peptidase) was increased after the short exposure but immediately decreased after the longer periods.

(*f*) The lipase (esterase) titer increased after the first two exposures but decreased after the longer period.

(*g*) The antiferment titer was quite irregular but gave evidence of a distinct increase after the final exposure.

(*h*) The diastatic activity fluctuated to a considerable extent, but, was as a rule, augmented after the roentgenray exposure.

It was apparent from the experiment that as a result of the roentgen-ray exposure the serum ferments were not only altered quantitatively, but that decided differences in reaction were obtained with different degrees of exposure and consequent stimulation of the liver parenchyma.

Intestinal Exposure. In the following experiment a dog of 19½ kilos was used. The diet was as follows:

Protein	330 gm.
Carbohydrate	130 "
Fat	35 "
Bone ash	40 "
Water	400 "

Because of the rejection of about 375 gm. of the diet on the two-day period following the second exposure the diet was reduced on July 24 to:

Protein	200 gm.
Carbohydrates	100 "
Fat	20 "
Saline	20 "

The water ration was increased to 600, later to 2000 cc per day.

The animal was rayed for periods of time similar to the first, but in this case the upper abdominal viscera were protected so that only the lower intestinal area was exposed. (Distance, 10 inches; 8 ma.; 6-inch spark; no screen).

(*a*) The weight of the animal decreased after the second exposure. This decrease, not associated with a corresponding increase of nitrogen excretion, was probably due to a loss of water content of the animal. The serum alterations revealed the following:

(*b*) A distinct transient increase in the non-coagulable nitrogen after the periods of exposure. There was no permanent alteration of the original amount (25 mg. per 100 cc).

(*c*) Only a slight and transient increase in the protease following the original exposure; no increase after the longer periods of raying.

(*d*) A considerable augmentation of peptidase, reaching the maximum after the second exposure; a decrease after the longest exposure.

(*e*) A lipase curve similar to that following the liver exposure.

(*f*) Marked fluctuations in the antiferment titer, with less evidence of reaction following the final exposure than in the case of the liver.

(*g*) A sharp increase in the diastase after the first two exposures; no change following the longest period.

On the basis of these preliminary experiments we have made a more detailed study of the serum changes following roentgenray exposure of the liver and intestinal and splenic areas in dogs. They were rayed for the following periods: five minutes, ten minutes and twenty minutes with Coolidge tube screened by a 3-mm. aluminum screen, 10-inch distance; 8 ma.; 5-inch backspark and a final unscreened exposure of twenty minutes. The time interval between the exposures varied from five to fourteen days. The exposures were made in the morning, serum samples being obtained before, one-half, five, twenty-four, forty-eight and seventy-two hours after the exposure. The samples were always taken before the animals had been fed.

The following observations were made:

Temperature.
Leukocyte count—differential.
Coagulation time—capillary tube method.
Urine: Volume. Total nitrogen excretion.
Serum enzymes: Protease.
Ereptase (peptidase).
Lipase.
Diastase.
Complement titer.
Antitrypsin titer.

Temperature Changes. The temperature of dogs is, of course, irregular, but we have made observations of the rectal temperature of animals in whom the liver, spleen and intestinal region were rayed.

With moderate dosage (five and ten minutes) little effect was observed, as will be apparent in the following records:

	Before raying.	30 minutes after.	1 hour after.	5 hours after.	24 hours after.
LIVER:					
Dog No. 10	102.0° F.	103.8° F.	102.4° F.	103.0° F.	104.6° F.
Dog No. 13	102.4° F.	102.4° F.	102.4° F.	102.8° F.	101.4° F.
SPLEEN:					
Dog No. 12	103.0° F.	103.4° F.	102.4° F.	102.6° F.	101.8° F.
INTESTINE:					
Dog No. 11	101.4° F.	102.8° F.	102.0° F.	101.8° F.	101.8° F.

When the longer dosage (twenty minutes, with or without screen) was given the temperature changes were of greater amplitude and consistency.

SPLEEN:					
Dog No. 8	101.4° F.	102.2° F.	103.6° F.	104.2° F.	102.0° F.

There was no apparent difference in the degree of reaction whether the splenic, intestinal or liver region was rayed.

The Leukocyte Count. The leukocytic reaction showed considerable differences with the different regions stimulated. In the following tabulation the normal count taken before the roentgen-ray exposure is contrasted with the average of the counts obtained for the half-hour, one-hour, five-hour, twenty-four-hour, forty-eight-hour and seventy-two-hour periods:

	Liver.	Spleen.	Intestine.
Normal	4,000	10,000	3,000
After five hours exposure	7,600	16,700	3.400
Before	3.200	14.200	3,000
After ten minutes exposure	5.600	13.400	8.200
Before	3.400	11.400	7.400
After twenty minutes exposure	10.000	11.300	12.900
Before	4.800	13.700	14.300
After twenty minutes exposure, (without filter)	8.100	14.300	17.450

In the first chart (I) the average leukocyte count (each curve representing the average of two dogs) following raying of the liver (*A*) splenic, (*B*) and intestinal, (*C*) areas for the various periods is shown. In these experiments the spleen dogs had a relatively high leukocyte count before the experiment was commenced. It will be observed that considerable differences in the type of response become manifest. The short sharp rise of the liver exposure is in contrast to the step-like effect of the intestinal exposure. Incidentally the latter reaches the maximum of reaction following the final exposure without filter. Raying of the splenic area evidently does not stimulate leukocytosis to any comparable degree. This corresponds in general with the observations previously recorded in the human and in experimental animals other than dogs.

The Differential Count. The differential count of the leukocytic response following the roentgen ray showed some variation, the chief difference being observed in a rather marked eosinophilia following the raying of the liver region. This effect is shown in the following table:

	Polymorphonuclear leukocytes. Per cent.	Small Mononuclears. Per cent.	Large mononuclears. Per cent.	Eosin. Per cent.
Normal	67	27	4	2.0
One-half hour after five minutes exposure of liver region	65	26	4	5.5
Five hours	77	15	3	4.5
Twenty-four hours	63	20	0	17.0
Forty-eight hours	62	21	6	11.0
Seventy-two hours	62	24	7	7.0

The eosinophilia reached its maximum after raying for 10-minute periods (average 11 per cent eosinophiles), but with the longer exposures was no longer so marked. It was observed in three of four dogs studied.

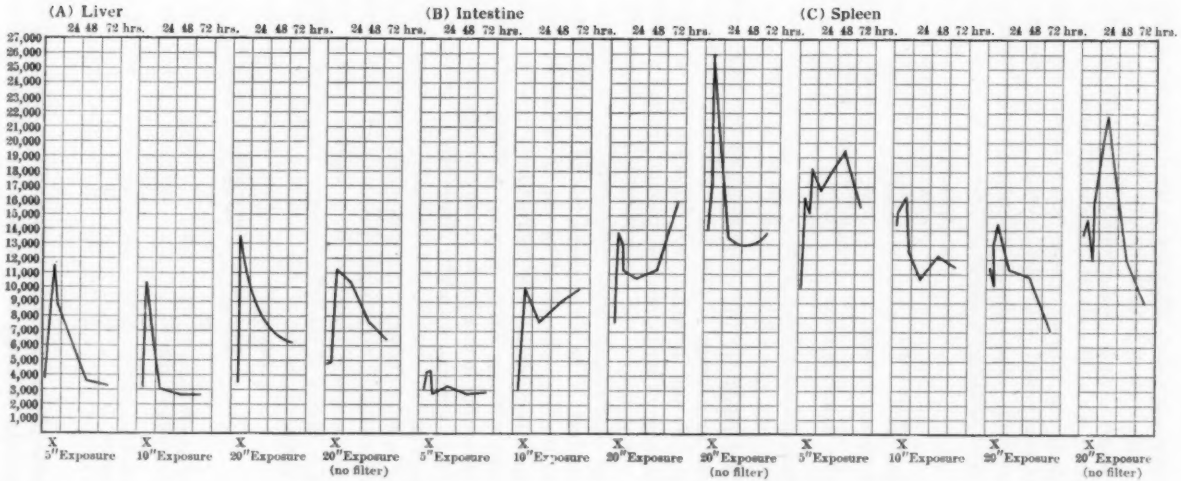


CHART I.—Effect of regional roentgenray exposure on the leukocyte curve.

Raying of the intestinal area and of the splenic area was followed by a fairly constant diminution of the mononuclear elements and a relative increase in the polymorphonuclear leukocytes. Nucleated red cells were occasionally observed in this group of animals; myelocytes seemed to occur more frequently in the blood after raying the liver, although a considerable number were observed after the more intense raying of the spleen.

Blood Coagulation. In studying the coagulation time we made use of capillary tubes drawn out to uniform caliber and the clotting time recorded when on breaking the tube a firm coagulum could be drawn out. A number of recent investigators, observing the reduction of the coagulation time following the raying of the splenic area have suggested that measure for therapeutic use in cases of hemorrhage. It is known that the raying of tumors and of lymphatic structures results in this effect on the coagulation. In our experiments the most prompt effect on the clotting time seemed to follow raying of the lower intestinal tract; the effect on the clotting time following raying of the splenic area was more delayed. In the latter case, however, the effect on the coagulation, especially after the longer raying periods, was more prolonged in effect.

In the following chart the average coagulation time is shown for the various periods:

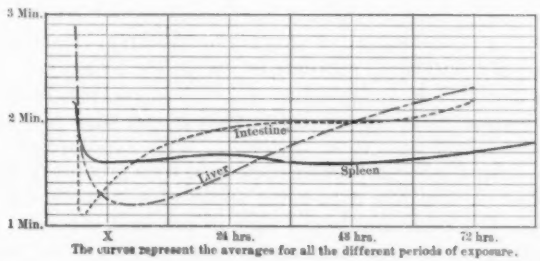


CHART II.—Coagulation time of blood after raying liver, intestinal and splenic areas.

Nitrogen Excretion. Kjehldahl determinations were made in duplicate of the urine nitrogen excretion. Using the relatively moderate doses of roentgen rays indicated we were not able to determine an increase in the excretion of nitrogen as a result of the exposure except in the case of the liver area, where raying for the longest time periods (twenty minutes) resulted in an increase of the average excretion:

Average for three days before raying	1.3 gm.
Average for four days after exposure (including day of raying)	2.1 "
Average for the next four days	1.7 "

Raying of the intestinal and splenic area had no such effect.

The non-coagulable nitrogen of the serum was never greatly altered, the only marked changes appearing in the serum after liver raying. The average NC nitrogen of the serum after ten minutes' raying was as follows (four animals):

	Normal, mg.	30 minutes after, mg.	1 hour after, mg.	5 hours after, mg.	24 hours, mg.
Liver area (per 100 cc) . .	21	23	31	30	29
After raying the intestinal area (three animals) (per 100 cc)	30	30	29	30	32
Splenic area (three animals) (per 100 cc)	17	18	17	17	17

With the longer periods of raying (twenty minutes with and without filter) the effects were even less apparent. Judging from Hall and Whipple's[23] results we may assume that we were dealing with relatively non-toxic doses, since in their animals which were given large and lethal doses the non-protein nitrogen of the serum was increased to a considerable degree.

Enzymes. *Protease.* Protease in the serum was determined by the chloroform method and the values represent the amount of nitrogen digest per cc in milligrams (twenty-four hours at 37° C.). It is apparent from a survey of the curves plotted in Chart III that differences in the extent of enzyme mobilization depended on the amount of roentgenray exposure as well as the area rayed.

The liver (III A) and intestine (III B) dogs had practically no protease present in the serum before raying and were not influenced by the smallest dose (five minutes). With exposure extended to ten minutes the intestine dogs responded by a prompt mobilization, the effect on the liver dogs being apparent as a somewhat delayed reaction, but persisting to the time of the next exposure. In this case exposure for twenty minutes again increased the amount of protease. A maximum effect for the liver exposure in these two dogs evidently lay between the ten and twenty-minute periods.

The spleen dogs (III C) differed to the extent that the initial serum titer tested before exposure contained a considerable amount of protease. (These two animals had an average leukocyte count of 10,000 as contrasted to the average of 3000 and 4000 for the intestine and liver animals.) Even the short roentgenray exposure resulted in a diminution of the titer, which, however, was recovered and even augmented before the second period of exposure. This second exposure (ten minutes) was followed by a slight increase and then a progressive diminution.

[23] Am. Jour. Med. Sci., 1919, **157**, 453.

Peptidase (Erepsin). The presence of a peptone-splitting enzyme in the serum has been reported at various times for several of the smaller laboratory animals as well as in the human. Our inability to secure glycyltryptophan compelled us to resort to Witte peptone, as reported in a previous paper (Petersen and Short[24]). The titer which we have used represents the minimum dilution of serum which in twenty-four hours' digestion still gives a definite tryptophan reaction with bromine water.

From a study of the curves (IV *a*, *b*, *c*) two distinct changes are apparent: First, that there is no correlation between the amount of proteolytic and peptolytic enzyme action in the serum. While in one increase a considerable amount of proteolysis may occur, there is no increase in the erepsin, or *vice versa*. On the other hand in periods when the one enzyme is increasing in titer the other enzyme may be diminishing its titer. (Charts III A and IV A.) Secondly, there is a decided difference in the response of ereptase with the raying of the different regions. The greatest and most persistent increase takes place following the raying of the gastro-intestinal tract. Raying of the splenic area seemed followed by least effect on the peptidase content.

Lipase. Serum lipase was titrated by the ethylbutyrate method and the charts represent the amount of free fatty acid liberated from 1 cc of ethyl butyrate by 1 cc of serum in twenty-four hours' incubation, and is expressed in terms of $\frac{N}{50}$ HCl. (Chart V, *A*, *B*, *C*)

Diastase (Amylase). Diastase in the serum was tested by the Wohlgemuth method, modifying the amount of the starch substrate (1 cc of 0.5 per cent solution of soluble potato starch), incubation being for twenty-four hours. It was found that the fluctuations of the diastase titer were very great, depending very probably on whether or not portions of the pancreas were included in the field of raying. The rôle of the pancreas, as well as other possible sources of blood amylase, has been discussed by King.[25] As a rule, raying of the liver area was followed by a greater mobilization of diastase than in the lower intestinal or splenic areas. In Chart VI the serum diastase expressed in Wohlgemuth units following a ten-minute exposure over the liver is illustrated.

Antiferment. Antiferment fluctuations following roentgen-ray stimulation were of considerable range, some of the exposures being followed by an increase and other by a decrease in the titer. In the table on page 118 (which shows the inhibition in percentage for the single serum unit, usually 0.025 cc serum, the antiferment alterations following raying of the splenic area are shown, together with the average.

[24] Jour. Inf. Dis., 1918, **22**, 147.
[25] Am. Jour. Physiol., 1914, **35**, 301.

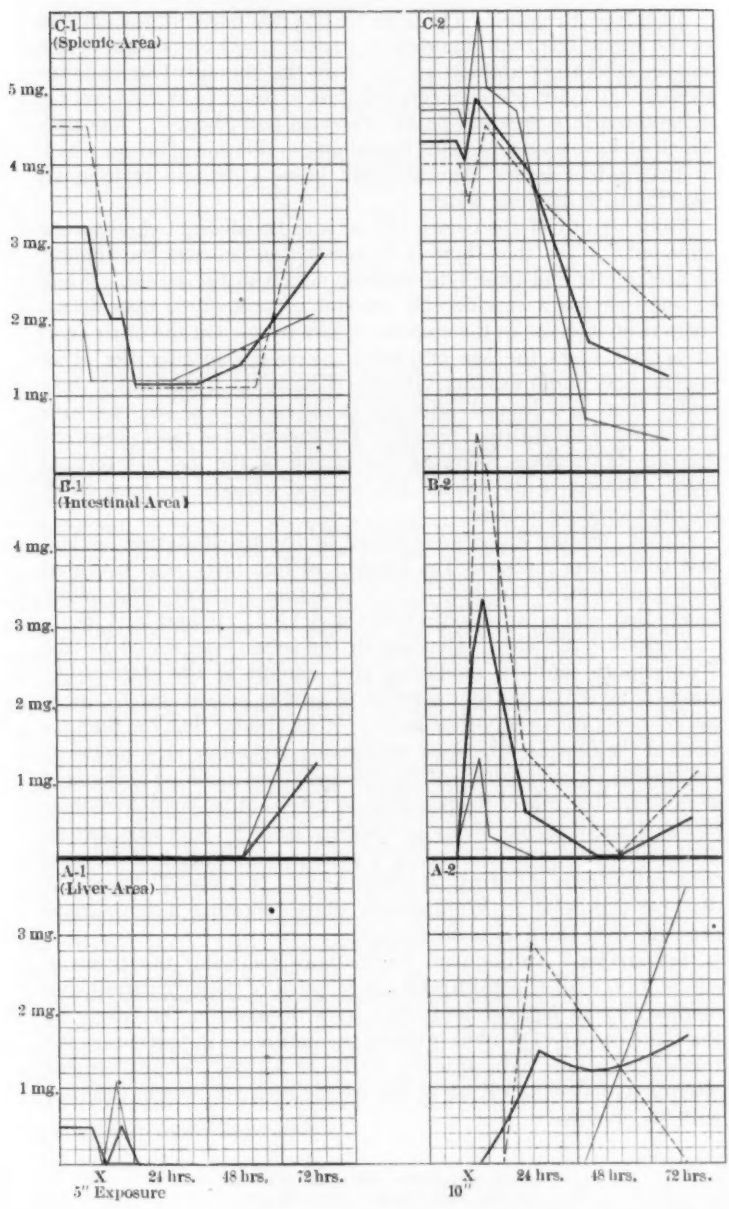
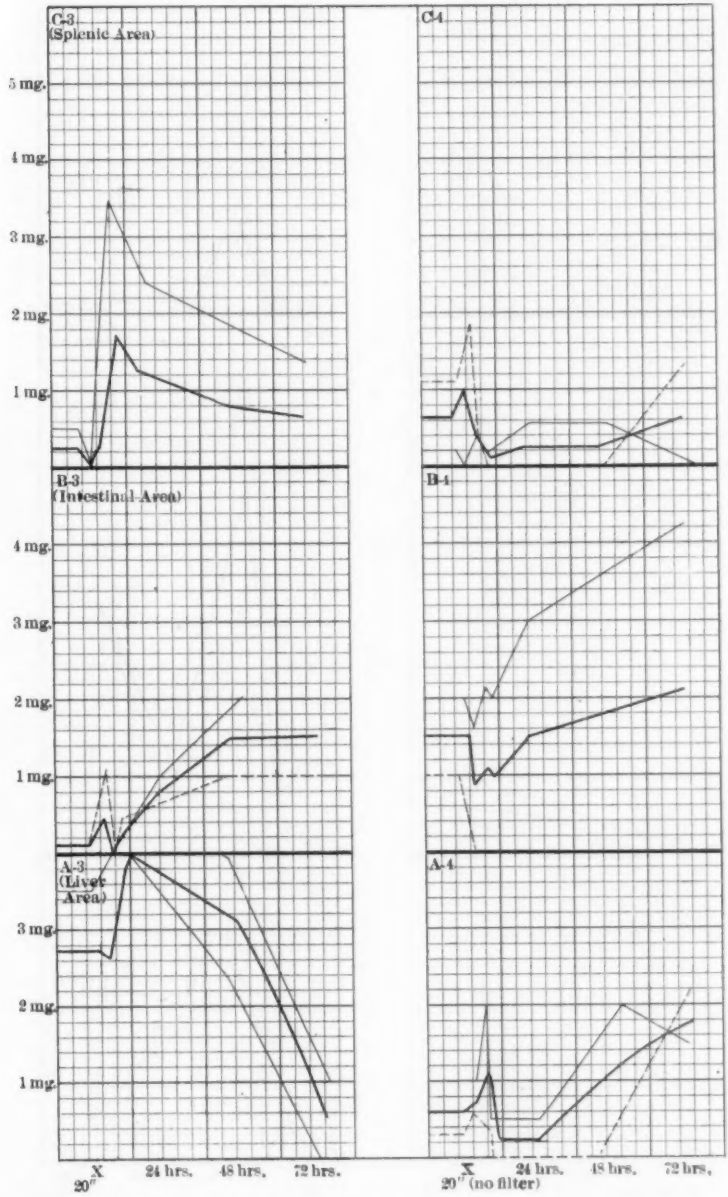


CHART III.—Mobilization of serum protease



following irradiation of various organs.

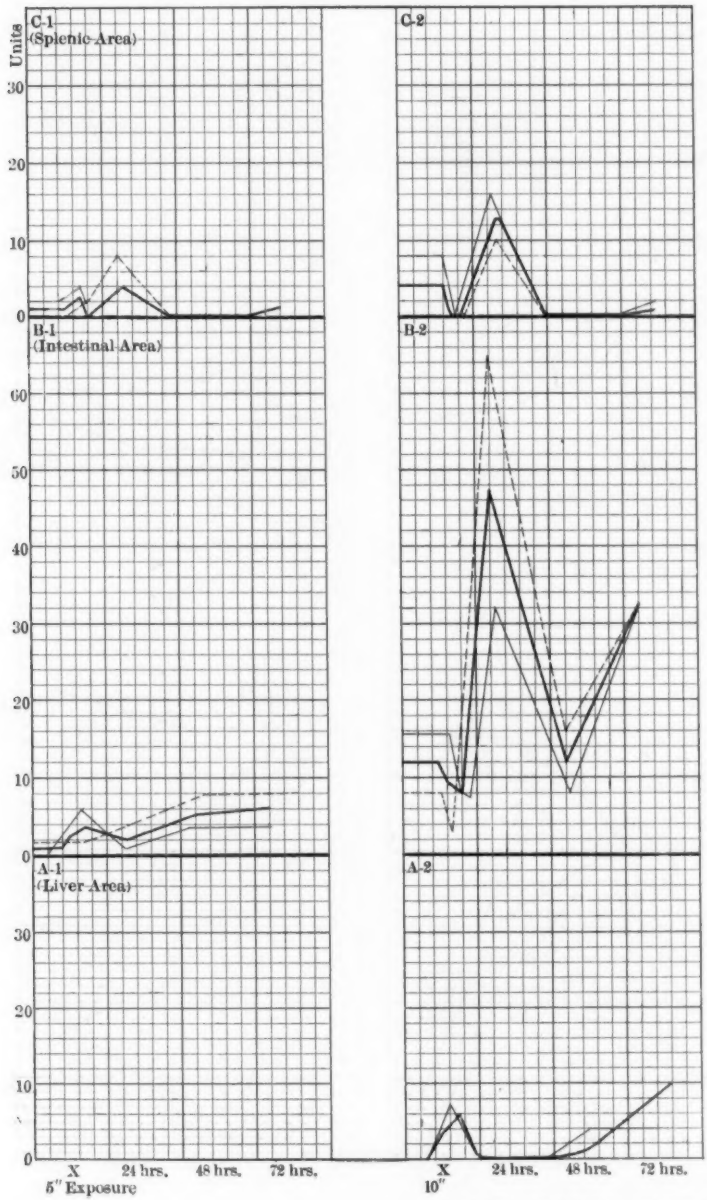
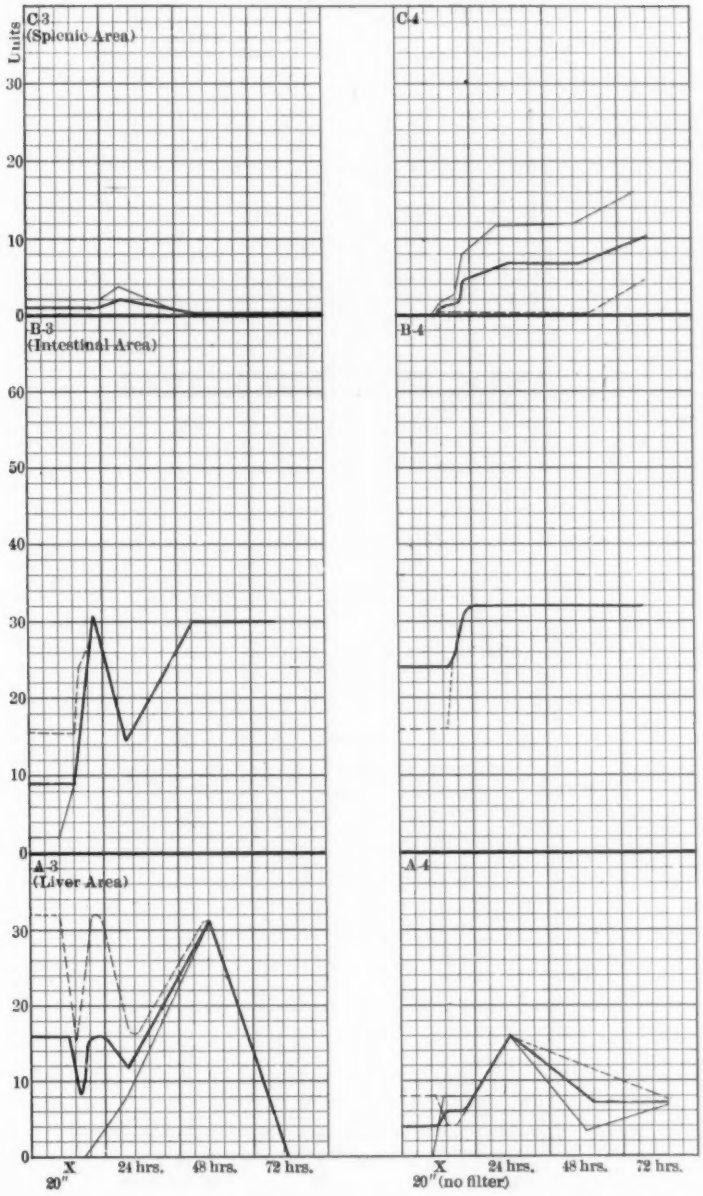


CHART IV.—Mobilization of serum



peptidase after regional irradiation.

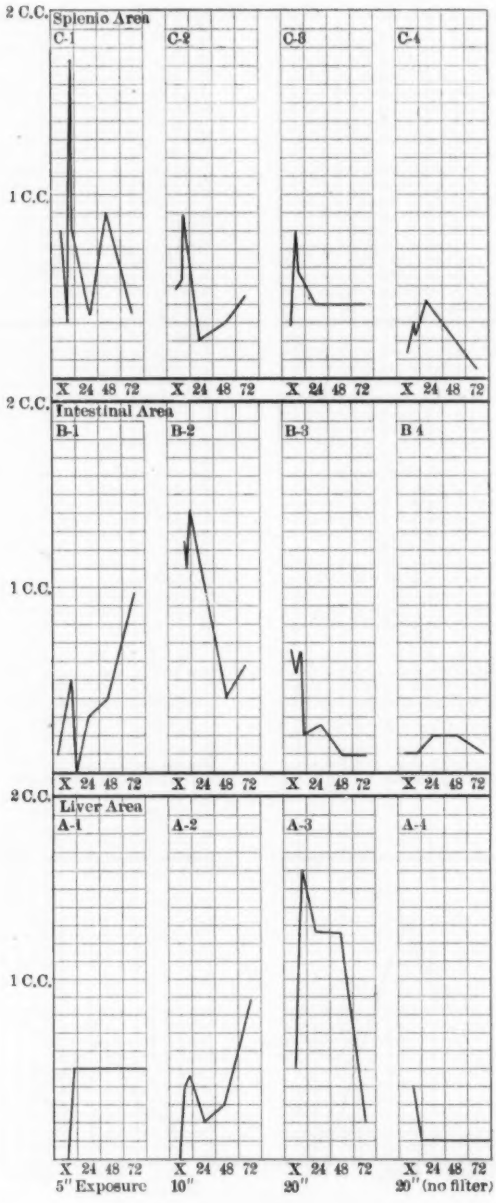


CHART V.—Lipase titer following regional roentgenray stimulation.

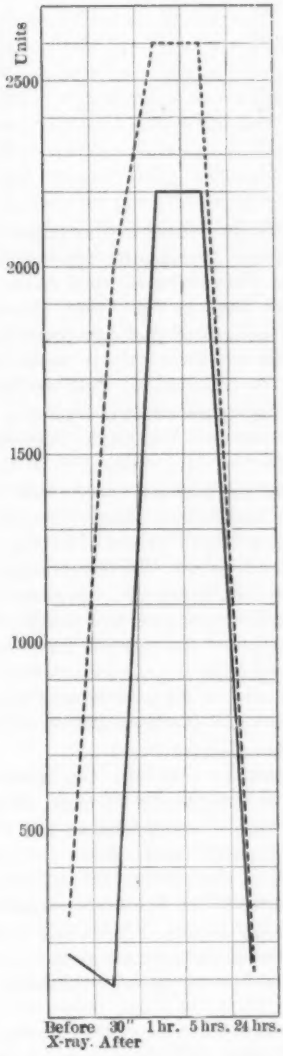


CHART VI.—Diastase titer following liver-raying (ten-minute exposure).

Before, per cent.	Minutes' exposure.	After 30 minutes, per cent.	1 hour, per cent.	5 hours, per cent.	24 hours, per cent.	48 hours, per cent.	72 hours, per cent.
0	10	50	0	50	20		
65	5	65	65	30	65	65	55
50	10	70	65	58	77	66	75
75	20	75	75	75	65	70	78
65	20	70	72	75	72	70	70
75	5	50	58	35	58	58	60
57	10	60	33	25	15	25	35
40	20	68	72	58	78	80	66
34	20	50	50	60	40	44	40
Average							
51		62	54	51	54	60	60

Discussion. The data presented in this paper seem to us to have a direct bearing on certain therapeutic applications of the roentgen ray and other related photodynamic and radiant agents, applications which heretofore seem to have been ignored because of the more obvious and direct uses of such agents in diagnosis or in local therapeusis. It is only in the relatively recent recognition of the value of heliotherapy in tuberculosis that we find evidence of this use of the indirect and systemic effect of a photodynamic agent.

Here the experience has been that such stimulation (heliotherapy) has a dual clinical effect in tuberculosis.[26] In the active case it is in general harmful because of an increased tendency to hemorrhage, augmentation of the temperature range, the amount of secretion, etc., all bearing evidence of an increase of focal activity of digestion of the connective tissue bulwark. In the quiescent case the clinical experience is, on the whole, favorable, the general resistance of the patient being apparently increased, the weight, the blood picture and subjective symptoms of the patient improved. This dualism in clinical effect we meet with in practically every agent used in the treatment of tuberculosis. We find it true of tuberculin. We find it true of the more recent non-specific methods: albumoses (Holler[27]), milk (Schmidt[28]), casein (Lindig[29]).

We are not yet familiar with the fundamental changes that underly heliotherapy or non-specific therapy, or specific tuberculin therapy for that matter. Very probable are the conclusions of Luithlen[30] and Starkenstein[31] and others that we have to deal primarily with changes in the permeability of the cells. According to this conception practically all the other recorded observations—changes in blood-forming organs, in clotting time, the fever and defervescence, the effect on the nervous system, on joints, liver and eye tissues, the increase in resorption of exudates, increase in mus-

[26] Pottinger, F. M.: Interstate Med. Jour., 1915, **22,** 818.
[27] Beit. z. klin. der Infektionskr., 1917, **6,** 92.
[28] Deutsch. Arch. f. klin. Med., 1919, **131,** 1, and with Krauss, Deutsch. med. klin., 1919, **15,** 503.
[29] Arch. f. Gynäk., **110,** No. 3.
[30] Loc. cit.
[31] München. med. Wchnschr., 1919, **66,** 205.

cular work and gland secretion, the increased resistance to intoxication—are merely the expressions in the various cell groups of such cell-membrane alterations. So, too, the enzyme mobilization which has been repeatedly suggested as the cause of the clinical improvement might be regarded as the result of the alteration in permeability.

With this in mind it seemed of some value to ascertain whether or not enzymes could be mobilized as a result of raying the abdominal organs, and if so, could qualitative differences be maintained by raying various organ complexes. The experiments here reported seem to bear out this assumption. Depending on the intensity of the roentgenray stimulation one can determine a maximum effect (which in our cases varied from ten to fifteen minutes' exposure), diminishing in either direction from a dose that was too small to cause appreciable differences (five minutes) to doses that were too large (twenty minutes to one hour). With these latter doses there was an actual diminution in the amount of serum enzymes titrated. Such a result is one that we might anticipate. Moderate doses will conceivably stimulate both cell activity in general and enzyme action itself, according to Richards's[32] experiments; larger doses would either leave that activity unaltered or result in an actual destruction of the enzymes.

In these experiments it is to be kept in mind that it is impossible to confine the roentgenray stimulation to any single organ. In raying the liver both the intestine and the pancreas would necessarily be included to some extent, as they would be, too, in raying the splenic area. In raying the intestinal area we endeavored to ray the lowest quadrant to avoid the simultaneous stimulation of other organs. It is also to be kept in mind that because of the duration of the periods of raying the blood and its elements must have passed through the rayed area many times. Some of the enzyme effect might have been derived from the leukocytes, which in the dog are relatively rich in proteolytic enzymes.

As previously stated, little attention has so far been paid to the possibility of organ stimulation by means of the roentgenray. Manoukhine[33] alone has carried out a series of experiments in tuberculosis. He rayed the spleen of tuberculous guinea-pigs and monkeys for varying periods and noted that such animals outlived his control animals for a considerable time, while animals in which the liver was rayed were unfavorably influenced. Manoukhine decided that when the spleen was rayed leukocytolysins were liberated, which, while destroying leukocytes, aided the organism in combating infection. When, on the other hand, the liver was rayed, leukocyte-protecting substances were formed and thrown into the circulation. Manoukhine treated a few human cases with encouraging results. Whatever the interpretation of the mechanism, these experiments

[32] Loc. cit.
[33] Wratsch Gazeta, 1914, **15**, 617.

bring the evidence that by means of selective organ stimulation therapeutic effects may be achieved.

The spleen and its relation to resistance to tuberculosis has in recent years been studied extensively, more particularly in connection with mononuclear-cell reactions and the effect of extirpation and roentgenray exposure thereto. It might seem possible that along with the cellular reaction the serum alterations suggested in this paper resulting from roentgenray stimulation of selected organs may have a part in the phenomena of altered resistance to tuberculosis.

Conclusions. By means of selective organ stimulation by roentgen rays in moderate dosage it seems possible to influence the serum enzymes to a considerable degree. Such doses act in stimulating a mobilization of various enzymes; large doses lessen the titer of the serum enzymes.

Raying the hepatic area in dogs resulted in a temporary leukocytosis (with eosinophilia) as well as a well-defined increase in the titer of protease, peptidase, lipase and diastase in the serum.

Raying the intestinal area resulted in a more persistent leukocytosis and a marked mobilization of peptidase; the other enzymes were altered less in proportion.

Raying of the splenic area was followed in general by a diminution of the serum enzymes with the exception of the lipase.

Alteration in the coagulation time of the blood following raying was not confined to raying of the splenic area but followed exposure of the other regions as well. No alterations of complement titer were observed following organ stimulation. The antiferment was usually increased after periods of raying.

THE RELATION OF THE PITUITARY GLAND TO EPILEPSY.

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Since the publication of Cushing's memorable monograph on the hypophysis,[1] increasing interest has been directed to the possibility of an endocrine factor or factors as the causative agent of those convulsions which are classed under the broad term "epilepsy." With further knowledge of the functions of these glands the body of evidence as reflected in the literature has rested on the pituitary element as the predominating factor in the so-called "endocrine epilepsies," although some writers following the lead of Laignel-Lavastine[2] believe the thyroid is the glandular element at fault.

[1] The Pituitary, 1911, W. B. Saunders Company, Philadelphia.

[2] The Internal Secretions and the Nervous System, 1919, Nervous and Mental Disease Publication Company.

For the past year every case of epilepsy coming to the Washington University Dispensary, St. Louis, and remaining under careful observation for a minimal period of three months has been studied from the point of view of a possible endocrine dyscrasia, more particularly one referable to the hypophysis. Our series consisted of 16 cases, representing all types and degrees of presumed epileptic convulsions without regard to any pre-supposed etiological factors except tumors. The average duration of the illness was five and six-tenths years, the extremes being six months and fourteen years.

Each case was investigated according to the following routine procedure:

1. Careful history.
2. Complete general including neurological examinations.
3. Mental tests using the Yerkes-Bridges point scale, in some cases correlated with the Binet-Simon tests.
4. Wassermann reaction on the blood and in several cases the spinal fluid.
5. Ophthalmoscopic examination of the fundus; tests of vision by the usual methods.
6. Visual fields by perimetry.
7. Lateral stereoscopic roentgen-ray plates of the skull.
8. Other examinations when indicated, such as cystoscopy, rhinoscopy, etc.

Before instituting treatment, some experiments to determine the relative potency of various commercial pituitary products were performed in the pharmacological laboratory through the courtesy of Dr. E. K. Marshall, Jr. Using as an index the amount of contraction of the isolated uterus of a virgin guinea-pig, according to the method of Roth,[3] we found a wide variation in the efficacy of the preparations on the market, and even of different lots of the same manufacturer. The least variable were found to be the posterior lobe extract of Parke, Davis & Co. (pituitrin) and the whole gland extract of Burroughs, Wellcome & Co (pituitary extract-whole gland), and these were adopted for this study.

All previous medication was discontinued and the patients were given varying doses hypodermically of one of the above-mentioned products or in a few instances the desiccated whole gland (Burroughs, Wellcome & Co.) by mouth. The average initial dose was 0.5 cc, increasing subsequently according to the tolerance of the patient. The number of ensuing attacks, the amount of pituitary substance administered, and the body weight were carefully charted and will be referred to later.

Before discussing our results a brief summary of each case, detailing only positive findings, may be of value.

[3] U. S. P. H. S. Hygien. Lab. Bull., 1916, No. 109.

CASE I (W. U. D., A29991).—Miss C. M., aged twenty-two years, whose family and past history were negative, has had convulsions since she was nine years old, during which time she had clonic spasms, more often on the right side. No auræ, hallucinations or delusions. Since her eighteenth year she has often had six attacks daily.

Physical Examination. Hypertrichosis of the upper lip and chin. Pupils equal, right slightly notched. Slight corneal anesthesia. Tongue on protrusion favors the right side. Cardiac examination showed occasional extrasystoles. Pulse-rate, 82. Blood-pressure, 115–80. Abdomen negative. Reflexes entirely normal. Mental examination showed what Dr. G. B. Smith termed a "typical epileptic constitution," with some scattering of the tests and retardation. Blood Wassermann negative (both antigens). Fundi normal. Lateral stereoscopic plates of skull (Dr. S. Moore) disclosed a small, long, shallow sella turcica. Clinoid processes drawn out into a point. The posterior portion of the skull increased in thickness and has general lack of detail in skull structures.

The patient was given an average of 1 cc of the posterior lobe extract weekly for two months, but the attacks became more frequent. Nine months later she reports feeling better since the treatment was discontinued.

CASE II (W. U. D., 38541). Master L. W., aged fifteen years, came of a normal family. Blindness had been discovered when thirteen months old. Attacks began a year ago, and there have been five subsequent convulsions, although for the past three months his mother states that the patient has had daily "spells of unconsciousness," but does not fall.

Physical Examination. Head small, high, narrow. No prognathism. Pupils small and equal. React to light but not to accommodation. Ophthalmoscopy showed a bilateral optic atrophy. Patient has faint light perception. Head otherwise negative. Chest and abdomen negative. Sparse axillary and pubic hair. Normal external genitalia. Blood-pressure, 92–60. Reflexes entirely negative. No Trousseau or Chvostek. No increased excitability to galvanic current. Astereognosis more marked at finger tips than in palm. No sensory changes. Mental tests were applied with difficulty, for there are few tests that fit a patient of this description, especially since he was unable to use his finger tips. There was evidently some mental deterioration not accounted for by his blindness. Deterioration probably progressive. Urine negative. Blood Wassermann negative. No record of roentgenograms of the skull. Posterior lobe given for four months. Whole gland subsequently administered for two months. During this period patient had eight severe and seventeen light attacks, so the treatment was discontinued.

CASE III (W. U. D., A8224).—Miss I. K., aged thirty-one years, whose family and past history were negative, has had epilepsy since she was twenty. Convulsions recently have occurred once or twice weekly.

Physical Examination. Facial acne (bromides?). Hypasthenic, rather emaciated. Examination quite negative. Blood-pressure, 96–75. Mental examination showed mental adult age of superior mentality as regards judgment and ability to work. Vision, both eyes, 20–24. Ophthalmoscopic examination: Disk edges blurred and irregular; retinæ pale but vessels normal; deep physiological cupping; visual fields normal. Urine negative. Phenolsulphonephthalein kidney functional test: First hour, 33 per cent; second hour, 13 per cent. Blood Wassermann negative.

Stereoscopic lateral plates of the skull showed practically an approximation of the anterior and the posterior clinoid processes, but no apparent bony bridging. Sella possibly a trifle deepened. Posterior lobe extract given for four months with no amelioration of symptoms.

CASE IV (W. U. D., A17278).—Mrs. M. J., aged fifty-two years, negress, had a normal family and past history. Onset of attacks four years ago, with subsequent monthly seizures unaccompanied by auræ.

Physical Examination. Pupils slightly irregular. Reactions normal. Teeth in poor condition (subsequently extracted). A small thyroid is palpable. Romberg, slight swaying. Examination otherwise negative. Blood-pressure, 120–84. Mental tests if anything above the average. If there is any retardation due to epilepsy it is quite slight. Vision: O. D., 20–15; O. S., 20–19. Ophthalmoscopic examination: Beginning cataract lower nasal quadrant of either lens. No abnormalities of the fundus. Visual fields normal. Urine negative. Wassermann on blood negative. Lateral stereoscopic plates of skull: Skull very long; edentulous mouth; sella normal. Posterior lobe extract administered for five months but attacks were not altered in severity or frequency.

CASE V (W. U. D., A31551).—Mr. L. R., aged twenty-five years. Father died of tuberculosis (?). When six years old the patient fell on his head and was unconscious for a time. Attacks since twelve years of age accompanied by dryness of the mouth. Now has weekly attacks.

Physical Examination. Entirely normal. Blood-pressure, 108–60. Vision: O. D., 20–30; O. S., 20–19. Ophthalmoscopy negative. Mental age that of adult. No retardation. Blood Wassermann negative. Visual fields normal. Lateral stereoscopic plates of the skull: There is a peculiar circular shadow above

the outer orbital process of the frontal bone. The object lies outside the skull. Otherwise negative. Given posterior lobe extract (see Chart I) by hypodermic twice weekly for two months. During this period he had five severe and thirty-six light attacks. The extract of the whole gland and the desiccated whole gland were then administered for seven months, during which the patient gained fifteen pounds. However, there were fifteen severe and thirty-seven light seizures, so the treatment was stopped.

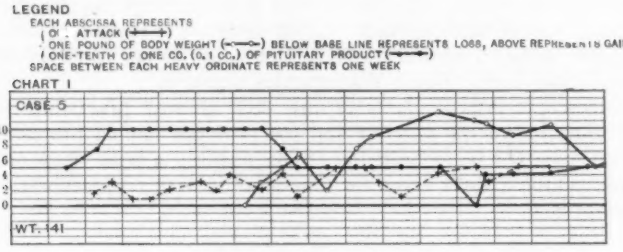

CHART I. Case 5.

CASE VI (W. U. D., A31684).—Mr. W. M., aged thirty-nine years, with a negative family and past history, has had epileptic convulsions for nine years not preceded by auræ. They occur at irregular intervals but are becoming more frequent.

Physical Examination. Several scars on head. Slight tremor of face. Teeth and gums in poor condition. Knee-jerk more active on the left. Other reflexes normal. Ophthalmoscopic examination showed normal fundi. Perimetry not done. Blood Wassermann negative. Mental tests showed a typical epileptic mentality with probably a primary mental defect. Scattering of tests, but good coöperation. Memory good for recent but poor for past events. Very emotional. Degeneration will be progressive and there is doubt of his ability to support his family. Lateral stereoscopic plates of the skull: Skull symmetrical, rather thin; sella rather small and its superior opening is very narrow. There are massive clinoid processes and calcification of the pineal body. Posterior lobe extract was given for three months followed by three weeks' administration of the extract of the whole gland, but there seemed no improvement, rather a more marked deterioration.

CASE VII (W. U. D., A16197).—Master L. S., aged sixteen years, had a normal family and past history. Has had monthly attacks for a year and a half. The convulsions are preceded by a severe headache, usually starting twenty-four hours before the attack.

Physical Examination. Left septal spur. Hypertrophied middle

turbinates. Small adenoid. Tonsils moderately enlarged. Visual fields normal. Vision of both eye 20–15. Ophthalmoscopy normal. Remainder of examination negative. Blood-pressure, 120–80. Blood Wassermann negative. Mental tests showed normal mental state with slight tendency to scattering. Extract of the posterior lobe was given hypodermically twice weekly for five and a half months (see Chart II), and the patient had no attacks. Following a visit to an exciting base-ball game he had four attacks resembling petit mal with no loss of consciousness. An episode of acute bronchitis resulted in a rapid loss of weight and five more attacks of a mild nature. A tonsillectomy was subsequently performed. The extract of the whole gland was substituted for four months, and there have been no ensuing attacks, but the patient has gained eight pounds in weight, or twenty pounds more than during his bronchitis four months before.

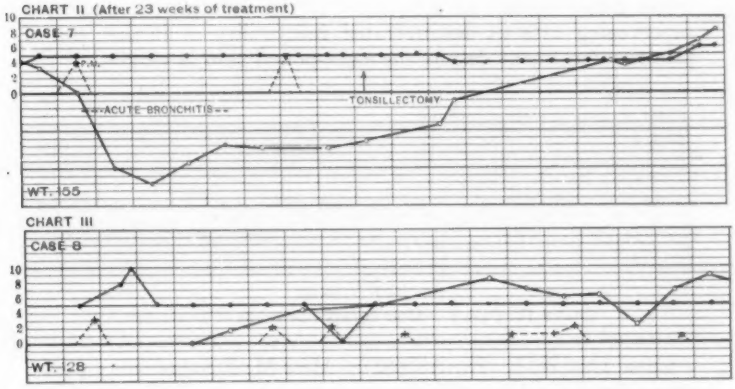

CHART II. Case 7.—After twenty-three weeks of treatment.
CHART III. Case 8.

CASE VIII (W. U. D., 29784).—Miss M. M., aged eighteen years. Her father was an alcoholic and died during an "epileptic fit." Mother has had five or six abortions. Ten brothers and sisters died during infancy—cause unknown. Oldest brother has epilepsy and another brother has very severe headaches (migraine?). Patient's attacks began five years ago and now occur monthly or oftener. Has had enuresis nocturna since early childhood. Some swelling of the feet and ankles recently. Delayed, irregular menses.

Physical Examination. Short, sthenic type. Sparse axillary hair. Breasts rather large. No evidence of hypothyroidism. Reflexes normal throughout. Uterus small, in second degree of

retroversion, movable. Adnexa negative. Chronic endotrachelitis. Cystoscopy showed a chronic trigonitis. Urine normal except a faint trace of albumin. Vision (both eyes), 20–15. Ophthalmoscopy, O. D., disk slightly pale, otherwise negative. O. S., disk normal. Perimetry disclosed a bilateral defect in the lower temporal field. Blood Wassermann negative. Mental tests normal. No deterioration or so-called epileptic constitution. Lateral stereoscopic plates of the skull: Skull generally thin; sella is small and the dorsum and posterior clinoid processes are bent forward and apparently bridge the fossa; the roof of the orbit and the great wings of the sphenoid approach the vertical; the frontal bone rises straight up anteriorly; the orbits are rather shallow (?). The diagnosis is suggestive of a mild degree of oxycephaly.

The administration of the posterior lobe extract was instituted for two months (see Chart III), followed by the exhibition of the whole gland (extract or desiccated) for six months, but numerous supervening attacks demonstrated the futility of further use of pituitary treatment despite the eight-pound gain in weight.

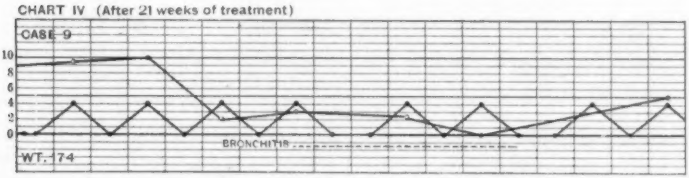

CHART IV, Case 9.—After twenty-one weeks of treatment.

CASE IX (W. U. D., A30683).—Mrs. M. Z., aged sixty years, whose family and past history were negative, has had convulsions for six or seven years, occurring every two or three weeks and preceded by vague feelings in the head. There is a definite history of polyuria, the patient claiming she passes three quarts of urine nightly.

Physical Examination. Facial aspect rather suggests an acromegalic, but there are no bony changes in the hands or feet. Ophthalmoscopy negative. Visual fields normal. Moderate emphysema. No arteriosclerosis. Blood-pressure, 100–70. Nervous system negative. Urine normal. Cystoscopy: Bladder negative; both ureters catheterized, negative; urine from both kidneys negative. Blood Wassermann negative. Mental tests show marked retardation that is not entirely accounted for by the language difficulty. No definite psychosis made out. Patient was given the extract of the posterior lobe for two months (see Chart IV) and three attacks occurred. The extract of the whole gland was then substituted and there have been no attacks in eight months.

CASE X (W. U. D., A14498).—Miss H. H., aged fourteen years. Father well. Mother has epilepsy and a positive (4 plus) Wassermann, and has had five spontaneous abortions. She has four children younger than the patient; one has "spasms." One child died of "marasmus." Present illness began a year ago, one week after an attack of "influenza." A second convulsion occurred four weeks later, and subsequently there have been attacks every two or three weeks. Tonsils and adenoids removed ten months ago.

Physical Examination. Thyroid slightly enlarged. No exophthalmos, tachycardia, tremor, etc. Further examination normal. Blood-pressure, 102–65. Vision (both eyes), 20–15. Ophthalmoscopy negative. Perimetry showed contracted fields for red and blue in the left eye. Right field normal. Lateral stereoscopic plates of skull negative. Both pituitary preparations were employed for four months, during which time there occurred thirteen severe and thirteen light attacks, although the weight remained almost constant. (see Chart V.)

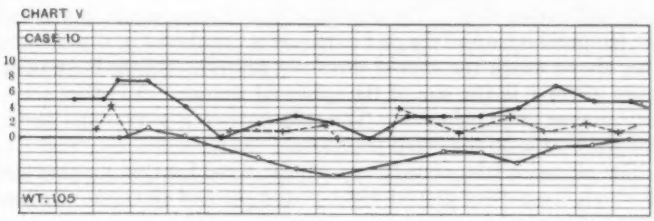

CHART V, Case 10.

CASE XI (W. U. D., A15143).—Mrs. C. R., aged forty-nine years. Married seven years. No pregnancies. Has had "typhoid fever" several times. "Nervous breakdown" seventeen years ago. Onset of convulsions three years ago. They now occur every month or two, but are not preceded by auræ. Frequent frontal headaches. Often has pain in epigastrium at no particular time of day. No relation to posture or food.

Physical Examination. Slight hypertrophy of the right inferior turbinate and more on the opposite side. Sinuses clear. Vision: O. D., 20–38; O. S., 20–30. Ophthalmoscopy negative. General examination negative. Gastric test meal normal. Sigmoidoscopy negative. Wassermann on blood negative. Mental tests showed normal reactions. Lateral stereoscopic plates of skull: Skull rather small; posterior fossa projects prominently downward and backward; otherwise negative. For four months the patient was given either of the two pituitary extracts. There were thirteen severe and twenty-five light attacks, while the weight decreased sixteen pounds.

CASE XII (W. U. D., 15324).—Mr. F. B., aged thirty-eight years, had a negative family and past history. Onset of epilepsy six years ago, with attacks of dizziness, but generalized convulsions did not occur until a year later. Seizures now once or twice weekly, sometimes once daily. Urinary frequency.

Physical Examination. Pupils rather small, equal and regular. React sluggishly to light. Accommodation reflex normal. Extrinsic ocular muscles negative. Heart showed slight general enlargement. Blood-pressure, 110–74.

Cystoscopy: Internal sphincter relaxed. Much tenderness in posterior urethra. Congested reddened trigone. No trabeculation. Ureteral orifices normal. Urine negative.

Vision (both eyes), 20–30. Ophthalmoscopy showed deep physiological excavation of disks. Perimetry showed normal fields.

Blood Wassermann twice negative. Mental tests showed characteristic epileptic constitution and marked mental deterioration. Deterioration will probably be progressive.

Lateral stereoscopic plates of skull: Skull contour very irregular and skull rather thin. The superior limit of the petrous portion of the temporal bone and the roof of the orbit are almost in a horizontal line, above which the clinoid processes project. There is an enormous increase in the size of the sphenoid sinuses. All other accessory sinuses seem enlarged. The sella turcica is very small and is bridged by the large clinoid processes.

The posterior lobe extract was administered for two months and although the patient gained eight pounds he had eleven severe and eight light attacks. During the previous year his average number of attacks under bromide treatment was for the same period nine severe and five light seizures.

CASE XIII (W. U. D., A32397).—Master H. H., aged thirteen years, had a negative family and past history. His first attack occurred a year ago, and he has had four subsequently.

Physical Examination. Small, active boy. Neurologically negative. External genitalia puerile in type. No pubic or axillary hair. Visual fields normal. Vision (both eyes), 20–15. Ophthalmoscopy negative. Mental tests normal. Patient is unusually bright. Wassermann on blood negative. Lateral stereoscopic plates of skull: Skull rather large, symmetrical; sella is small and shallow with large clinoid processes which approach each other. The patient was given extract of the posterior lobe for five months during which his weight remained constant and he had no attacks. Treatment was then discontinued. Four and a half months later his mother reported that he had had no further attacks and was growing taller and stouter.

CASE XIV (W. U. D., A33465).—Mr. B. B., aged thirty-two years, had been married twelve years and had four healthy children.

A sister, four years old, could not walk or talk, otherwise his family history was negative. Past history of no importance. Fourteen years ago the patient had his first attack and a second followed a year later. They now occur every three weeks and there are no auræ. Six months ago, for no reason known to him, there began a rapid increase in weight, forty pounds to date.

Physical Examination. Revealed a large, rather stout, but healthy appearing man. There was a fair hair distribution with an increase of adipose. Right pupil larger than the left. Both react well to light and accommodation. Neurologically normal. External genitalia normal. Vision (both eyes), 20–12. Ophthalmoscopy negative. Visual fields normal. Psychic study by Dr. B. C. Marshall showed normal behavior and good insight. Blood Wassermann negative. Lateral stereoscopic plates of the skull: A large hooked process at the external occipital protuberance, otherwise negative. The posterior lobe extract was given for a month followed by two weeks on the desiccated whole gland. As he had no attacks he discontinued further treatment. Seven and a half months later he reported having lost twenty pounds, but was in good health, although at times he became very nervous. There have been no further attacks.

Case XV (W. U. D., A33339).—Miss V. R., aged thirteen years, who had a negative family and past history, has had for the past year and a half momentary spells, when her "mind seemed to leave her," although she was not dizzy and did not fall. First convulsion occurred eight months ago and there have been numerous ones since.

Physical Examination. Entirely negative. Vision (both eyes), 20–12. Ophthalmoscopy negative. Blood Wassermann negative. Mental examination showed no abnormal reactions. Mental age normal. Lateral stereoscopic plates of skull: Skull symmetrical; a slight degree of convolutional atrophy throughout; sella clearly defined and within the limit of normal dimensions. Diagnosis: Increased intracranial pressure. The patient was sent to the St. Louis Childrens' Hospital for further study. While there the spinal fluid was found to have a normal cell count and colloidal-gold curve. Wassermann on blood and spinal fluid negative. Von Pirquet negative. Complement-fixation for tuberculosis 2 plus. Another roentgen-ray examination of the skull suggested oxycephaly. There were no convulsions while in the hospital. The whole gland extract was administered for two and a half months and while she gained six pounds eight attacks occurred.

Case XVI (W. U. D., A39768).—Miss E. C., aged seventeen years, had a negative family history. When four weeks old she had numerous convulsions and her life was despaired of. The attacks then ceased. Six years later there developed a right-sided paralysis

(hemiplegia?). Could not walk, talk or use the right arm. In six weeks she was able to walk. Since then she has always been nervous, but recovered from the paralysis. Nine years ago, during a thunder-storm, she had convulsions. Six months ago while abed with "influenza" she became unconscious. Since that time she has daily attacks which she describes as "choking in the throat." They occur two to six times daily, but there are no auræ or convulsions.

Physical Examination. Rather undeveloped. Does not appear her age. Small thyroid palpable. No pulsation, bruit, etc. Cold extremities. No dermographism. Vision (both eyes), 20–19. Ophthalmoscopy negative. Visual fields normal. Mental tests: Grades up to a normal mental age level; marked memory defect both for numbers and words. Lateral stereoscopic plates of the skull: Skull long and not deep; sella small and shallow; very large dorsum sellæ and posterior clinoid processes; roofs of the orbit approach the vertical and join the inner table of the skull well up on the posterior aspect of the frontal sinuses; all accessory sinuses are large. Diagnosis: Indeterminate, suggestive of acromegaly of incomplete type.

The extracts of the posterior lobe and of the whole gland were given for two months. At the termination of that period the patient stated that the attacks are slightly less severe, although there is little change in their number. She feels much stronger, although there has been an intervening attack of mumps.

In analyzing the foregoing cases we attempted to use as criteria for study the following points:

1. Symptoms or physical signs referable to the hypophysis.
2. Abnormalities in mental reactions.
3. Roentgenographic changes in the sella turcica.
4. Fundus changes.
5. Abnormalities of the visual fields.
6. Body weight.
7. Number and character of the attacks.
8. General health of the patient.

1. *Symptoms or Physical Signs Referable to the Hypophysis.* Five cases (31 per cent of the total) displayed one or more features possibly ascribable to pituitary changes, and it is interesting to note that Tucker[4] in his larger series had the same incidence. The patients presenting these changes were (1) Case I, hypertrichosis of the chin and upper lip. (2) Case VIII, short, sthenic individual; abnormal fat distribution; sparse axillary hair (delayed, irregular menses) suggested an incomplete dystrophy adiposo genitalis. (3) Case IX, polyuria; acromegalic facies. (4) Case XIII, small stature; infantile genitalia; no pubic or axillary hair. (5) Case

[4] Tr. Sect. of Nerv. and Ment. Dis., Am. Med. Assn., 1919, p. 169, also Arch. Neurol. and Psychiat., 1919, **2**, 192.

XIV, gain of forty pounds in six months; body contour and fat distribution suggested a hyposecretion of the posterior lobe.

2. *Abnormalities in Mental Reactions.* These were found in 6 cases (37 per cent) and varied from scattering of tests, retardation, memory defects, to marked mental deterioration. Three patients (19 per cent) showed what Dr. Smith terms a "typical epileptic constitution." He characterizes this group by their feeling of superiority, their superciliousness and diffidence. They are emotional, suspicious and irritable, and these differences are accentuated before attacks (see Cases I, VI and XII).

3. *Roentgenographic Changes in the Sella Turcica.* Discussion has been rife concerning the changes about the pituitary fossa demonstrable by the roentgen ray, and any consequent pressure or other effect on the contained gland. Johnston and his associates [5, 6, 7] claim that in essential (*i. e.*, "idiopathic") epilepsy there is a condition of "local acromegaly" characterized by large clinoid processes, roofing of the fossa, increased density of bony tisssues forming the roof of the orbits, etc., and claim to have found one or more of these features in a very high percentage of cases. Timme[8] insists that roentgen-ray changes in the sella are not indicative of pituitary lesions, but claims that such a feature as "a closing in of the sella turcica" may be found. However, Munson and Shaw[9] think there are no constant changes in the pituitary gland from an anatomical point of view in these subjects, and the former author[10] as a result of autopsies on 85 epileptics at the Craig Colony draws the following conclusions: "The sellas from a series of unselected epileptic subjects present a wide variation in type. The average size seems a trifle smaller than the figures given for normals and the contained gland seems to weigh less. Roofing will be seen in the roentgenogram, but in reality the gland is well exposed and pressure seems a remote possibility. Bony changes are present but seem to be the anomalies which might well be present in a similar series of non-epileptic cases. There is no characteristic change to be seen in epileptic sellæ."

After these important observations by Munson it is noteworthy that 8 cases (50 per cent) in our series showed sellar changes (Cases I, III, VI, VII, VIII, XII, XIII, XVI), but that only 3 (Cases VII, XIII and XVI) improved under pituitary treatment. Two patients (Cases IX and XIV) who had unquestioned evidence of pituitary disturbance, and who did well under the gland administration, had roentgenographically normal sellæ.

[5] Am. Jour. Roentgenol., 1914, n.s., **1**, 172.
[6] New York State Jour. Med., 1916, **16**, 559.
[7] Pennsylvania Med. Jour., 1914–15, **18**, 429. Also Jour. Nerv. and Ment. Dis., 1914, **41**, 495.
[8] Arch. Neurol. and Psychiat., 1919, **2**, 240; Arch. Ophth., 1920, **49**, 268.
[9] Arch. Int. Med., 1914, **14**, 393.
[10] Ibid., 1918, **21**, 531.

4. *Fundus changes* were displayed by 3 patients (Cases II, III, VIII); 1 instance of slightly pale disks, 1 in whom the disk edges were blurred and irregular with pale retinæ and 1 case of bilateral optic atrophy.

5. *Abnormalities of the visual fields* were discovered in only 2 cases (VIII, X), 1 of whom showed a bilateral temporal defect and the other a unilateral contraction of the fields for red and blue. If, as is contended by Bell,[11] Cushing,[12] Engelbach and Tierney[13] and others, these "pituitary epilepsies" are due to pressure against the uncinate gyrus, it would seem rational to anticipate evidence of similar and coincident pressure on one or both of the optic nerves, probably at the chiasm, but the low evidence of changes in the fundi or visual fields, as found in this and other studies of epilepsy, would militate against such a hypothesis.

6. *Body Weight.* Numerous authors have noted loss of weight when pituitary gland was administered over long periods, some claiming that emaciation ensues. Bell[14] found that a few guinea-pigs gained weight during pituitary feeding and Burch[15] reports a patient who gained while taking the anterior lobe, but these findings are not correlated with other essential data or controls, and hence are of doubtful value.

In our series the weight curves presented wide variations, irrespective of the type of product employed, the increase or diminution in the number of attacks and without any dietary change by the patient. As a matter of fact there was a lower average gain by the cases that improved (0.77 pound per week) than in the unimproved patients (1.66 pounds per week).

Gain in weight .	6 cases (37 per cent)	(Cases V, VII, VIII, IX, XII, XV)
Stationary . .	5 cases (31 per cent)	(Cases II, IV, X, XIII, XVI)
Loss	4 cases (25 per cent)	(Cases III, VI, XI, XIV)

The changes in weight were about evenly divided between the improved and unimproved cases, as follows:

Improved Cases: Gain, 2 cases (Cases VII, IX). Stationary, 2 cases (Cases XIII, XVI). Loss, 1 case (Case XIV). Gain per patient per week, 0.77 pound.

Unimproved Cases: Gain, 4 cases (Cases V, VIII, XII, XV). Stationary, 3 cases (Cases II, IV, X). Loss, 3 cases (Cases III, VI, XI). Gain per patient per week, 1.66 pounds.

7. *Number and Character of Attacks.* There seems to be considerable variance of opinion concerning the efficacy of pituitary treatment in stopping or diminishing the attacks. Clark[16], [17] and

[11] The Pituitary, 1919, Baillière, Tindall & Cox, London.
[12] Ibid., 1911, W. B. Saunders Co., Philadelphia.
[13] Medicine and Surgery, 1918, **2,** 466 and 549.
[14] Loc. cit. The Pituitary, 1919, Baillière, Tindall & Cox, London.
[15] Journal-Lancet, Minneapolis, 1920, **40,** 53.
[16] Jour. Am. Med. Assn., 1914, **63,** 1652.
[17] New York Med. Jour., 1914, **99,** 5.

Prior and Jones[18] report no success from this method of procedure. Timme[19] holds that feeding with the anterior lobe alone "produces marked improvement and even cures the disease" in many epileptics of the Froehlich dystrophy type; and Joughin[20] reports a case of this group. Tucker[21], [22] states that "good results with pituitary feeding need be expected only when the patient has some clinical evidence of hypopituitarism, and this should be backed by roentgenographical evidence."

How fallacious this line of reasoning is has been demonstrated by the fact that there were 5 cases (31 per cent) that improved definitely under treatment, and of this class 2 showed evidence of hypopituitarism and 2 others showed no roentgen-ray evidence of change in the sella turcica.

It was curious that none of our patients had so-called "uncinate attacks," and in fact few had any auræ, and none had auræ of an olfactory or gustatory nature.

The number and character of attacks in the unimproved cases were apparently not influenced by the treatment. In several instances there were more numerous seizures than when the patient had been under the influence of bromides, but there seemed no progressive increase as a result of the pituitary products, nor in any case was a change observed in the type of the attack. However, in several of the improved cases it is possible that the major fits alone were diminished. Thus Case XIV reports feeling "nervous" frequently, which may represent the equivalent of petit mal attacks, and Case XVI insists that while there seems no decrease in the number of attacks they are diminished in severity.

It might be apropos to state here that our experience with the amount of pituitary substance to be administered, while naturally varying with the size and age of the patient, has convinced us that in those cases amenable to this therapy much smaller doses (0.5 cc once or twice weekly) than are usually employed will prove sufficient. Conversely, in those patients not improved any amount of the gland may be used without more satisfactory results.

8. *General Health of the Patient.* This has proved of little prognostic value, for, as a rule, the patients did well under observation, and, as has been shown above, the average gain in weight was slightly greater for the unimproved cases than for those who were benefited by the treatment. Two of the improved cases developed attacks of acute bronchitis (see Charts II and IV) during the treatment, but despite a rather rapid loss in weight soon regained their previously augmented weight level.

[18] Jour. Ment. Sci., London, 1918, **64**, 30.
[19] Arch. Neurol. and Psychiat., 1920, **3**, 601.
[20] New York Med. Jour., 1916, **104**, 693.
[21] Virginia Med. Semi-Monthly, 1916–17, **21**, 1.
[22] Tr. Sect. of Nerv. and Ment. Dis., Am. Med. Assn., 1919, p. 169, also Arch. Neurol. and Psychiat., 1919, **2**, 192.

Conclusions. While our comparatively small series of cases and the length of time they were kept under observation do not permit us to be dogmatic, the following conclusions seem justifiable:

1. Certain cases are apparently benefited by pituitary gland administration. In our series 5 cases, or 31 per cent.

2. The preferable product seems to be the extract of the whole gland, and the most satisfactory mode of treatment is hypodermically.

3. No cases showing the "typical epileptic constitution" were benefited.

4. There was no improvement in those patients with abnormalities of the fundi or visual fields.

5. Neither physical signs referable to the hypophysis, mental reactions (except the "typical epileptic constitution"), changes in the sella turcica demonstrable by the roentgen ray or variations in weight or health offered any criteria by which the relative degree of success or failure of the treatment could be predicted.

My thanks are due to Dr. Sidney I. Schwab for many helpful suggestions, and to Dr. G. B. Smith who performed most of the mental tests.

NOTE.—On account of the length of this article a number of the charts have been omitted.

REVIEWS.

THE CLINICAL STUDY AND TREATMENT OF SICK CHILDREN. By JOHN THOMSON, M.D., F.R.S.P. (EDIN.); Honorary Member, American Pediatric Society; Consulting Physician to the Royal Edinburgh Hospital for Sick Children; formerly Clinical Lecturer, Diseases of Children, University of Edinburgh. Third edition. Pp. 887; 249 illustrations. London: Oliver & Boyd, 1921.

THE third edition of this book has been enlarged to three times the size of the first edition. While covering the entire field of diseases of children the bulk of the text is devoted to clinical methods, clinical signs and symptoms and descriptions of those diseases which are either peculiar to children or show characteristics in children different from those occurring in adults. Little space is allotted to pathology, by which feature the author makes his work distinctive from the majority of books on the subject. By doing this he renders the book more attractive for those interested in the everyday treatment of sick children. The methods and diseases considered are those included in the ordinary conception of disorders of childhood, the subjects being arranged by chapters devoted to the diseases of the various anatomical systems. As a whole the subject-matter has been brought up to date as well as is possible, considering the many valuable contributions that are being made to pediatric knowledge constantly, and almost from day to day. Due to the time that must be devoted to the many processes incident to revision, it is understood that no book can be absolutely contemporaneous. Notwithstanding this allowance the occasion must be taken to specifically criticise the failure of any mention or allusion to the Schick test, which has been developed a sufficient number of years to warrant the addition of this method which has opened up avenues of prophylaxis and treatment of the greatest value. A. E. S.

SURGICAL CLINICS OF NORTH AMERICA, PHILADELPHIA NUMBER. VOL. I, NO. 1. By PHILADELPHIA CONTRIBUTORS, February, 1921. Philadelphia: W. B. Saunders Company, 1921.

THIS, the maiden number of the *Clinics*, sets a standard for the succeeding numbers. The work is published bimonthly and should meet with unqualified success, judging by this first example.

An introduction to the work is written by Dr. W. W. Keen, in which he briefly outlines medical and surgical advances since 1860. Following this are eleven contributions by some of the leading surgeons of Philadelphia, after the custom laid down by similar earlier works; most of the articles are transcriptions of a clinic. However, in many instances the writer has elaborated upon his subject and presented a striking monograph. Such an article is the one by Deaver on Pancreatitis; also J. G. Clark, C. H. Frazier, T. T. Thomas, and others, on special subjects.

These are the things that will appeal to the *Clinics'* readers, and it is to be hoped that the standard will be continued. The inclination is always present to give all the minutiæ and details about isolated cases. This makes for voluminous and ofttimes irrelevant reading. These articles are singularly free from this fault and consequently are interesting, instructive contributions, well presented and full of meat. E. L. E.

TEXT-BOOK OF TRACHEOBRONCHOSCOPY (TECHNICAL AND PRACTICAL). By SANITÄTSRAT DR. M. MANN. Translated by A. R. MOODIE, M.A., M.D., CH.B. (ST. ANDR.), F. R. C. S. (EDIN.), with 50 illustrations and 5 plates in the text, 10 colored plates in the Appendix. New York: William Wood & Co., 1921.

FROM the foreword of this book we quote the following: "Six years have elapsed since the appearance of the German edition of this book. No advances of importance have been made, either as regards the method itself or in its application." Is this an apology by the translator for having delayed so long in bringing this German work to the English-speaking otolaryngologist, or an indication of his attitude toward tracheobronchoscopy?

As a manual for the student or for the beginner in endoscopic work this book is scarcely adapted. The lack of detail in the chapter on anatomy and the comparatively small space given to technic presupposes more or less knowledge on the part of the reader. In the description of technic the author confines himself to the use of the Brunings's appliances, believing that these instruments are so superior to those of any other make that they are alone worth consideration. He does, however, give a fairly good history and description of a large number of the different tubes, forceps, applicators, and other instruments used in the various clinics of the world, especially those of Germany.

The second part, which is called "The Practice of Tracheobronchoscopy," occupies practically five-sixths of the text of the book, and consists of a careful review of the literature published up to the time of the appearance of the German edition, and is a systematically arranged compilation of abstracts. The illustrations of

the instruments are mostly from catalogues, with a few original photographs. There is also a series of colored plates which are interesting solely from a pathological standpoint, perhaps with one exception, where views through the bronchoscope are very accurately drawn and colored.

As an aid to those who are interested in the literature of the subject this book will be found very useful, but scarcely so for the student who desires to learn the practice of endoscopic manipulation.

G. B. W.

TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION. VOL. XXXVIII. Pp. 709; illustrated. Philadelphia: William J. Dornan, 1920.

THIS volume of the *Transactions* contains the papers, forty-two in number, read before the Association at the meeting held May 3, 4 and 5, 1920. Several of these papers are on the subject of empyema and its treatment. These, taken with the free discussion, bring out some very useful and illuminating points. One other subject has more than one contributed paper, namely, the thyroid gland.

Every article is of first quality, and when written by men such as compose the American Surgical Association, we have a collection that is well worth not only reading but close study. E. L. E.

HISTORY OF THE PENNSYLVANIA HOSPITAL UNIT (BASE HOSPITAL NO. 10, U. S. A.) IN THE GREAT WAR. Pp. 253, illustrated. New York: Paul B. Hoeber, 1921.

AN erstwhile historian records that when the British Army evacuated Philadelphia, in 1778, the military authorities carried off with them the bedding, instruments and medicines belonging to the Pennsylvania Hospital which they had been using for some two years In this present record of returning good for evil we have a most interesting account of the services of a group of Pennsylvania Hospital men taking over a British base hospital at one of the Channel resorts and for nearly two years serving the sick and wounded of the English Army The book portrays the details of organization, preparation, transport, the care of some fifty thousand sick and injured, the manifold activities about a base hospital in time of war, and the return home. P. F. W.

SURGICAL ASPECTS OF DYSENTERY. By ZACHARY COPE, B. A., M.D., M.S., F.R.C.S., Surgeon to Bolingbroke Hospital, Hunterian Professor, R.C.S., etc. Pp. 157; 19 illustrations. London: Oxford University Press, 1920.

THE literature of the surgical aspects of dysentery is scanty, scattered and not readily available. This fact has led the author to collect the information and to supplement it with his own experiences of 2000 cases and the combined experience and information gained from others of much wider observations.

The subject is treated thoroughly, beginning with a chapter on pathology and its relation to the surgical complications. Differential diagnosis is discussed at some length, especially the question of recognizing the difference between an appendicitis and a dysenteric typhlitis or appendicitis. Amebic abscess of the liver is treated rather extensively in four chapters. Remote lesions such as iritis, parotitis, arthritis are all discussed. E. L. E.

KEEN'S SURGERY. VOLS. VII and VIII. EDITED by W. W. KEEN, M.D., F. R. C. S., Emeritus Professor, Jefferson Medical College, Philadelphia. Pp. 1800; 996 illustrations, 29 of them in colors. Philadelphia and London: W. B. Saunders Company, 1921.

THESE two volumes contributed by surgical experts bring this great system up to date. They really are the great practical lessons of the War, put into organized form available for civil surgery and have added every worth-while achievement in surgery since the War. The very last word in surgical principles and practices is also included. The volumes are really a series of monographs by the masters of the various subjects discussed, and consequently the reader gets the very latest, best, most scientific and practical consideration of each and every subject. Then there is the added advantage that the editor has arranged, pruned and edited in the true sense of the word the entire composition.

A separate desk index volume to the entire work of eight volumes makes instantly available every detail on any subject.

It is throughout a most wonderful work—instructive, scientific, engrossing; at the same time most easy and pleasant reading because of the smooth style and diction. E. L. E.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Mobilization of the Elbow by Free Fascia Transplantation with Report of Thirty-one Cases.—MacAusland (*Surg., Gynec. and Obst.*, 1921, xxxiii, 223) says that ankylosis of the elbow results either from an infectious process or from traumatism. The latter is usually a fracture-dislocation with wide separation. The large amount of callus which forms as a result of this injury at first interferes mechanically with motion. Later an ankylosis results, usually fibrous in character. The infectious process may be either acute or chronic. The causative agent is usually the streptococcus, the pneumococcus, or the gonococcus. The onset is sudden and the course severe, ending usually in a bony ankylosis. On the other hand, the focus of infection is situated elsewhere, and the joint condition is caused by the hematogenous deposits in the joint either of attenuated bacteria or of toxins. The ankylosis results from adhesions within and without the joint and is, at least first, fibrous. In the elbow no position of ankylosis is favorable to function and any position is ungainly. No attempt at mobilization should be made until epiphyseal growth has ceased. Where the joint has been the seat of an infectious process, arthroplasty should not be done until all sign of active progress has ceased. As a rule one should not wait too long, as convalescence is lengthened where atrophy of the soft parts from disuse is marked. The operative technic is given. If there is no evidence of infection the cast should remain intact for a week. Passive movements are begun in ten days. The arm is always kept above a right angle. Gentle massage is instituted in three weeks, while baking is inaugurated after six weeks.

Gastric Operations.—Barrington-Ward (*Lancet*, August 20, 1921, p. 382) says that numerous theories of ulceration have been advanced—oral sepsis, embolism, intestinal stasis. The author gives at length the recent mechanical theory of Waugh—an abdomen in which the colon is abnormally mobile is a pathological abdomen and as such is more prone to pathological processes than the normal type. The abnormal

mobility is the predisposing cause. The exciting cause is the pull of bands and ligaments. Waugh has successfully treated formed ulcers of stomach and duodenum by colopexy only. The problem of dealing actively with the ulcer is still before us, for the majority of ulcers have progressed so far that natural repair cannot be expected. Gastro-enterostomy is a most valuable operation, but has been very much abused. The clear indications for its performance are: Gastric stasis due to organic obstruction of the stomach; an ulcer of the stomach or duodenum which may be afforded rest and allowed to heal by a short-circuiting of the food path. The absolute contraindication is an atonic dilated stomach. The author has found that the further from the cardiac end and the nearer to the duodenum the ulcer was situated the better were the final results. The final results of simple excision are disappointing and cannot be compared with those of partial gastrectomy, for excision has a higher mortality, is a difficult performance and often leaves a deformed hour-glass stomach. Partial gastrectomy has excellent final results. It removes an ulcer especially prone to malignant change. Two cases in the routine examination of the specimens showed early carcinoma. It is more certain to cure symptoms than gastro-enterostomy alone. The operation the author employed for partial gastrectomy is essentially the Billroth II method. Complete abdominal exploration was attempted in every case with special search for right iliac fossa abnormalities. The appendix was taken routinely. Cholecystectomy was done in three cases for gall-stones.

A Note on the Treatment of Secondary Hemorrhage from Branches of the Common Carotid Artery.—BLAIR (*Ann. Surg.*, 1921, lxxiv, 373) says that secondary hemorrhage of the carotid artery and its branches is to be prevented by not suturing wounds that extend through the floor of the mouth and by packing or freely draining all wounds in the neck above the level of the thyroid cartilage that contain a ligated primary branch of the carotid artery. Secondary hemorrhage from a ligated primary branch might possibly be controlled by previously having placed the ligature as far from the carotid as possible and when bleeding actually occurs to free the stump from the surrounding indurated tissues and secondarily to ligate any branches that are given off proximal to this ligature and if necessary to loosely religate the stump itself as far from its origin as possible. If it is found necessary to place the ligature on the bleeding stump so close to the external carotid as to preclude the formation of a proximal clot, then the external carotid itself should be exposed and a ligature placed on each branch and on the trunk at least an inch from the bifurcation in the hope of establishing a permanent clot in the external carotid itself.

Gunshot Injuries to the Brain.—SWANBERY (*Am. Jour. Roent.*, 1921, iii, 445) says that 3 of 11 cases reported died. Four cases had been operated upon, the foreign bodies removed. Three died from meningitis, giving an operative mortality of 75 per cent. Of the 8 living cases, 7 still have foreign bodies in the brain and 5 of these have Jacksonian epileptic attacks. The 1 patient who lived, following the removal of the foreign body has had no convulsions. All the cases except 1, however, complain of headaches or vertigo. About half the cases have paresthesia at times in the formerly para-

lyzed parts, although the paralysis itself has disappeared in most of the cases. The special symptoms are due to the traumatized portion of the brain through which the foreign body has passed to reach its final place.

The Value of the Various Methods of Bone Grafting Judged by 1930 Cases.—McWilliams (*Ann. Surg.*, 1921, lxxiv, 286) says that there are three requirements for a successful bone graft; bridging of the defect; size and type capable of reëstablishing the circulation and stimulus to osteogenesis. The osteoperiosteal method offers a very large area of raw bone, hence it is to be preferred to all other methods of grafting. From a study of 1930 bone graftings the author concludes that the bony defect should be filled in with small bone chips and on one or two aspects, overlapping the ends of the fragments, covering in the bone chips, should be placed one or two strips of periosteum with adherent osseous plaques, taken from another bone. This method is applicable to large as to small bony defects. The cause of many non-successes is due to ineffective immobilization or to undue curtailment of its duration. From four to six months' immobilization is ordinarily required for complete success. There is sufficient evidence to prove that the most effectual treatment of non-union of fractures is bone-grafting. Despite some opinions to the contrary, bone-grafting should not be performed in infected fields. The causes of failure in bone graftings are improper methods of grafting, suppuration, insufficient immobilization, fracture and dislocation of the grafts, and atrophy of the ends of the bone to be grafted. The author states that the intramedullary method of grafting should be discarded.

Old Os Calcis Fractures.—Cotton (*Ann. Surg.*, 1921, lxxiv, 294) says that os calcis fractures are of interest because they give so large a percentage of cripples and because these cripples are strong men as a rule in youth or vigorous middle age. The author judges that total disability for real work seems to be the fate of something like one-third to one-half the cases. He lays more emphasis upon remodelling than impaction for the resulting impaction is not mechanically first-rate as a rule. The treatment essentially has been developed with the idea of clearing away excess bone, on the outer side, removing spurs and limbering up joints by manipulation. The main features are similar in all the author's cases—shortened and flattened heel which is not touched in the repair measure; outward dislocation which calls for section of the calcis behind the post-astragular junction—spurs sometimes outgrowths from an original fragment, sometimes newly grown. They are removed very liberally as are all common osteophytic spurs. In the author's crippled cases the main pathology is the outward broadening due to the shoving outward of the peroneal plate of bone and to bone growth behind it associated with loss of some part of lateral motion constantly. The fracture is a crushing fracture with irregular cleavage lines and unusually massive bone replacement—a broad shapeless bone which has lost all chance of rocking under the astragulus. The key to the whole question is doing enough surgery. In his latter cases he has cleared away all excess bone deep below the cortical layer. In doing this clearing, he cuts across the post-astragular-calcaneal joint, regardless of ligaments and of joint capsule.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

A Rapid Method for Determination of Water-soluble Vitamine B.—BERMAN (*Jour. Am. Med. Assn.*, January 29, 1921) prepares the synthetic medium in which yeast cells are to be grown with and without the water-soluble vitamine B by adding saccharose 20 gm., ammonium sulphate 3 gm., calcium chloride 0.25 gm., potassium acid phosphate 3 gm., asparagin 3 gm. and magnesium sulphate 0.25 gm., to distilled water, and this solution is made up to 1 liter. This is then sterilized at 10 pounds' pressure and stored in the refrigerator. To 30 cm. of this synthetic medium in a graduate is added 1 c.c. of a Fleischmann yeast-cake measured and cut as 1 by 1 by 1 cm., and the whole is rubbed up with a glass rod until a complete and uniform suspension has been obtained. One-half of the suspension is then placed in the centrifuge tube graduated in tenths of a cubic centimeter and the other half is poured into a 15 c.c. centrifuge tube similarly graduated. To one is added a portion of the vitamine-containing solution, measured out into amounts of from 0.1 to 0.5 c.c. The tubes are then stoppered with non-absorbent cotton and incubated at body temperature. After twenty-four hours the cotton stoppers are withdrawn and the yeast cells thrown down in an ordinary centrifuge for a few minutes. An excess of growth will be found in the tube containing the vitamine and the reading can be compared with the control tube. As the amount of excess growth varies directly with the amount of vitamine a relative determination of this substance in the solution or in permanent uniform suspensions is practical. This relative value is called the vitamine B index, and it is obtained per cubic centimeter of solution by this equation: $\frac{1}{\text{amount of vitamine solution}} \times \frac{\text{reading of vitamine tube}}{\text{reading of control tube}}$. It is necessary first to render the milk protein-free by the method of Osborne and Mendel.

Stools and their Relation to the Feeding in Infants.—GROVER (*Jour. Am. Med. Assn.*, February 5, 1921) recommends that the stools be examined in the napkins in which they are passed. He says that the high protein stool is the result of a small proportion of fat and a high proportion of protein in the food rather than to too much protein, and is not a mark of indigestion. Its most characteristic feature is the shiny surface produced when the tongue depressor is passed through it. This shine must be differentiated from the glistening appearance of mucus, and also from the natural moisture of all freshly passed stools due to the water content. This type of stool is dull on the outside where the napkin touches it. The most typical high protein stools are produced from feedings of fat-free milk, undiluted and boiled hard

for three minutes. Besides showing the gloss they are very smooth when pressed out with the tongue depressor. They also appear to be transparent, the nap of the cloth being visible through the thin part of the stool. The stools are a shade of olive green. Soap in the stool is formed from the neutral fat taken by the baby which is broken down into fatty acids which readily unite with bases readily accessible in the intestine. The form of fat when absorbed by the intestine is soap and possibly also fatty acids. The intestine absorbs the most of the fatty acids and soap, but a small proportion passes out as a stool. If the fat in the formula is high and the protein is low there will result a typical soap stool, which is of very light color. They are usually dry and constipated and rarely average more than two a day. When spread out they appear smooth and dull. The granular soap stool differs from the normal soap stool in that the surface is granular when spread out with the stick. The granules are small masses of soap surrounded by mucus. They may be very minute or as large as pin-heads. The large granules are macroscopic but are also small fat curds surrounded by mucus. Starches in the stool are readily stained by the use of iodine or Lugol's solution. The particles of undigested starch stain blue or black. Stools containing much fermented starch are loose, acid, light brown, contain mucus and excoriate the buttocks. This type of stool is most likely to be found in babies having indigestion from certain of the proprietary foods. Indigestion of sugar presents no typical stool. They are frequent, very acid, excoriating and very watery. The solid parts are usually full of small air-bubbles formed by the chemical decomposition. These stools are usually green and those from maltose-dextrin preparations are usually brown, while those from sucrose or lactose fermentation are green.

Mental Disorders in Children Following Epidemic Encephalitis.—LEAHY and SANDS (*Jour. Am. Med. Assn.*, February 5, 1921) report six cases varying in age from five to fourteen years. Of these four were boys and two girls. Their mental status was characterized by purposeless, impulsive motor acts, marked irritability, definite attention disorders, distractibility and changing variable mood, inadequate and inconsistent emotional reactions, marked insomnia, and in two cases precocious sexual feelings and intense eroticisms. The writers believed that these mental disorders can best be explained on a purely physical basis. While there was no pathological material upon which their opinion was based, reasoning by analogy from cases which showed similar lesions, such as are seen in true African sleeping sickness, in general paralysis and in subacute infections of the brain tissue, they arrived at this conclusion. The replacement of the destroyed tissue by neuroglia scar tissue acts as a stimulating and undoubtedly as an irritating agent to the rest of the nerve tissue. They further believe that the resolution of the mesodermic inflammatory reaction takes place over a relatively prolonged period and causes considerable irritation to the remaining relatively normal nerve cells. The irritation to the cell bodies results in the function of these cells with the production of the usual effects of the functions of such cells. There are, as a result, both sensory and motor disturbances and marked conduct disorder. The patients may be in the chronic stage of the disease, but this is prob-

ably not the case, because the patients physically showed no evidence of any disease process and all somatic manifestations of disease processes were absent.

Periodic Vomiting with Acetonemia.—MARFAN (*Arch. de méd. des enf.*, January, 1921) says that the recurring attacks may occur at intervals of weeks, months or years and that there is no regularity about their occurrence. This condition was first described by Gruere in 1840, but the author claims that he was the first to call attention to the acetonemia in 1901. He pointed out a familial tendency and that this vomiting with acetonemia may occur in the course of some other malady and thus obscure the diagnosis. He claims that the primary cause is not in the alimentary tract but in some primary metabolic disturbance which causes the acetonemia. In the few cases that have come to autopsy the fatty degeneration of the liver and other signs of violent acute intoxication resembled those of chloroform poisoning. d'Oelsnitz found four children in one family with periodic vomiting with acetonemia. Two of these died in these attacks. The author himself had three patients who had been under observation for more than ten years who never had more than one typical attack. Between the ages of two and six the attacks are most frequent and most severe. After six years the frequency and intensity decline and the age of twelve years seems to be the final limit. Among sixty adults known to have had periodic vomiting with acetonemia in childhood four have attacks of migraine, two young women have had attacks of gall-stone colic after marriage and one man developed diabetes. During the attacks the urine contains large amounts of ketone bodies, but during the intervals the urine is normal. The attacks of vomiting may alternate with attacks of asthma or with transient fever or sometimes with somnolence with pronounced acetonemia or with convulsions, with stupor and sometimes with meningitic symptoms. One child of eighteen months developed convulsions after the attack of vomiting with somnolence or coma lasting for a week and leaving a flaccid paralysis for over a month. This child later had a recurrence of the vomiting with acetonemia.

Statistics on the von Pirquet Reaction.—GITTINGS and DONNELLY (*Arch. Ped.*, February, 1921) reviewed twenty-seven cases found to be tuberculosis at autopsy. Sixteen of these had positive von Pirquet reactions and eleven had given negative reactions. They say that the clinical designation of generalized tuberculosis with meningitis depends upon the terminal meningeal infection. Generalized tuberculosis without meningitis usually is diagnosed as a pulmonary disease because of the extent of the pulmonary involvement. Since the tuberculin test is of clinical value only in the first year or two of life and the sputum is difficult to obtain there is justification of error. The distinction between infantile atrophy, chronic gastro-enteritis and non-tuberculous bronchopneumonia on the one hand and pulmonary tuberculosis on the other, may be extremely difficult in the presence of a negative tuberculin test. The margin of error should be reduced by repetition of the test. Unless the history and course be characteristic of the type the possibility of tuberculous spondylitis should always be considered in the

differential diagnosis of a spinal paralysis. This series demonstrates the high percentage of tuberculous infection and the comparatively low incidence of recognizable clinical tuberculosis in children. It is to be emphasized that there should be more than one repetition of the von Pirquet test if the first is negative.

OBSTETRICS

UNDER THE CHARGE OF

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Nitrous Oxid-oxygen Analgesia and Anesthesia in Normal Labor and Operative Obstetrics.—DANFORTH (*Pennsylvania Med. Jour.*, March, 1921, p. 383) gives his experience in 1700 cases of labor in which nitrous oxide has been used. At the beginning of the second stage of labor the administration of gas is begun. In multiparæ it is usually begun a little before the beginning of the second stage, and this may be done with primiparæ who bear pain badly. A mask is placed over the face and the patient instructed to breathe deeply and rather quickly. Usually from three to eight respirations are needed to get the effect of the gas. In some instances gas is given throughout the length of the pain. If the anesthetist watches the patient it can readily be ascertained how many inhalations are needed to produce an effect, and this can be given throughout the labor. When once the patient feels the effect of the gas the mask can be removed and the relief from pain will continue throughout the length of the uterine contraction. It is important that the gas should be given immediately when the pain begins. If the pain becomes severe gas will not give complete relief. The percentage of oxygen added to nitrous oxide varies from five to fifteen, according to the necessity of each individual patient. The average percentage varies from five to eight. Before delivery patients do not rebreathe the gas. It is well to keep the patient under a condition of analgesia and not to let her pass into the anesthetic state. Should the latter be present struggling is much more likely to occur. If the proper percentage of oxygen is added cyanosis will be avoided. At the moment of expulsion it is well to add a small quantity of ether during the last three to five pains. This relaxes the muscles, decreases to some extent the violence of uterine action, which makes it more easy to control the passage of the head and prevent laceration. Under this episiotomy can readily be performed without inflicting pain. Just at the moment of expulsion the patient should be made completely unconscious with ether, from which she will quickly arouse. The administration of gas or ether is not a matter for an untrained person. Experience shows that analgesia is more difficult to secure and maintain than is anesthesia and that experience and training are necessary for both. When analgesia is properly produced it does not tend to lessen the vigor

or frequency of the pains; when anesthetics are skilfully administered during the second stage of labor the uterus often acts very vigorously and efficiently because relieved of the depressing influence of suffering. Consciousness need not be lost and the patient may assist very greatly by spontaneous effort. When the patient is nervous and excited and helping herself not at all the administration of gas often has a most happy effect. Even if the patient does not deliver herself, by its use she may carry on to the point where a simple forceps operation is all that may be needed. The use of gas during labor prevents exhaustion and patients recover very much more rapidly after confinement and with much less nervous prostration than if suffering is not relieved. The writer believes that the danger of postpartum hemorrhage is lessened by gas anesthesia. The uterine muscle is not relaxed as much under gas as where more complete anesthesia is obtained. In toxic cases it is thought of great advantage to avoid the irritating effects of ether and chloroform upon the organs of secretion. The writer has been unable to observe complications on the side of the child arising from the use of gas in labor. Cyanosis has been no more frequent than before gas was used. In reviewing a little over 530 labors there were 17 cases in which the child was lost. Nine died shortly after birth, eight were stillborn. Of the nine, six were premature, from six to eight months; one was one of a pair of twins and the other stillborn. One of the premature children born at seven months had also a cleft palate. Another living for a part of the day had a congenital heart lesion. Another had at birth an abdominal tumor, which turned out to be an enormously large bowel. Autopsy showed there was an obstruction of the sigmoid due to a peritoneal band caused by peritonitis which had occurred before birth. The mother had a severe attack of influenza during the pregnancy. In the case where pregnancy was complicated by a large fibroid in the lower uterine segment Cesarean section was performed, the child dying two days after birth from an unknown cause. This mother had no gas as the section was performed under ether. Among the stillborn children one had syphilis; another was one of a pair of premature twins—one was lost because the cord prolapsed, although version was done at once in the effort to save the child. There were two deaths among infants occurring in difficult high forceps delivery under ether, and there was one other fetal death, an anencephalic monster.

In operative obstetrics the problem is very different. Analgesia is rarely indicated, while surgical anesthesia is needed in all cases. Gas anesthesia is useful, when skilfully administered, in operative cases. It is not sufficient to give its administration into the hands of an obstetrical nurse untrained in anesthesia or some other untrained person. Even for surgical anesthesia the writer believes there is no anesthetic which is safer or more satisfactory within its proper field of use than nitrous oxide. When improperly given there is none more unsatisfactory and also to some extent dangerous. So far as apparatus is concerned none is perfectly satisfactory. None of these machines seem to be based on a knowledge of the physiology of the circulation and respiration. Under these conditions it is not strange that inexperienced persons often fail in producing good anesthesia. Primary perineal repair is probably the most frequent surgical operation in

obstetrics. Gas anesthesia is useful for this and rebreathing may be practised if necessary. A little ether may be added should occasion arise. It is sometimes difficult in these repair operations to keep the patient quiet because profound anesthesia is not needed, and with less the patient may become restless and struggling. Nitrous oxide allows the patient to wake with little or no nausea and does not tend to relax the uterus. In the low forceps operation anesthesia by gas has been found sufficient. If relaxation is not satisfactory ether may be added. The writer induces labor by means of a dilating bag. Nausea is usually avoided by using gas, especially if the patient is given no breakfast on the morning of the day in which the induction of labor begins. The writer uses bags to induce labor and would even give the patient analgesia for this manipulation. He believes that when a patient is perfectly conscious, if she has got self-control she can sometimes aid somewhat in this process. In incomplete abortion, curetting or packing may well be done under gas, and there is usually no difficulty in controlling the patient. For version the writer would rely upon ether, as considerable relaxation of the uterus is required. For Cesarean section the writer has used gas, with special success in eclamptic or toxic patients, as he believes the organs of elimination are less damaged than with ether or chloroform. Believing that an anesthetic which would dissolve fatty acids would injure a toxic patient the writer has used gas for some time. In this administration special care is necessary.

Cyanosis must be avoided, as otherwise the child will be injured, while the patient must be sufficiently asleep to permit manipulation. When the abdominal wall is completely relaxed there is danger that the bowel may be extruded. He does not believe that a preliminary injection of morphin is necessary in these cases, and he has found that the uterus contracts better during Cesarean section under gas than under ether. Cases in which the patient is in a very bad condition and in which the uterus must be quickly emptied are difficult to manage. Such an instance would be the pernicious vomiting of early gestation, where the patient is highly toxic. If the pregnancy is advanced to two and a half or three months the writer would perform anterior vaginal hysterotomy under gas, and has seen nothing but good results. The writer does not believe our methods of analgesia and anesthesia ideal, but his experience has shown that at present gas is a most valuable agent for some, at least, of the suffering which occurs in parturition. He believes that it injures the organs of elimination little if at all. He would not neglect methods of general attention, which often help the patient to bear the suffering of the first stage of labor. The value of morphin given by hypodermic injection has long been recognized. While the writer has had good results in the use of gas he does not believe that ether can be entirely discarded. Gas does not secure great muscular relaxation, and the attempt to do this will be followed by disappointment. Too much has been claimed for gas anesthesia and bad results have sometimes occurred. When gas does not obtain relaxation sufficiently ether must be added; and if a considerable quantity be required the results are not always satisfactory. The value of a skilled administrator cannot be overestimated. In discussion the point was brought out that just before the child is born it is well to give pure oxygen only for a few moments. This seems to avoid any tendency to cyanosis in the

infant. Respiration is established more slowly in the child after this procedure, but ultimately the child will breathe well. The same thing may be done in Cesarean section at the moment when the uterus is incised and the child delivered. So also patients who have received morphin before operation will benefit by pure oxygen. Cases of eclampsia are also benefited by this method. In forceps cases the operator must be careful not to begin traction with the forceps before the patient is completely relaxed. If the effort to extract the child is begun too soon no aid is secured from the uterus.

While the reviewer has had an experience similar to that of Danforth in many respects, he has also been led to believe that in highly toxic patients gas is a very dangerous remedy. In these patients the action of the heart is greatly disturbed and the second sound may be largely lessened or even abolished. Gas is sometimes rapidly fatal to such a patient. The safest anesthetic for use in all the requirements of obstetric practice is ether and oxygen. If these are combined by an experienced anesthetist the reviewer has seen no emergency in obstetric practice which could not safely be met by such anesthesia skilfully given.

GYNECOLOGY

UNDER THE CHARGE OF

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Radiotherapy of Fibroids.—Until within the most recent past the treatment of fibroids has been exclusively surgical and the results achieved have been eminently satisfactory. Every decade has seen a material reduction in the mortality after operations for fibroids, but even in the hands of excellent surgeons there is yet an average mortality of from 3 to 5 per cent, and if we consider all the cases operated upon we would probably find a considerably higher percentage. Contrast with this the fact that radiotherapy has a mortality of zero. To be sure the word "cure" means something different in the two methods, according to GELLHORN (*Jour. Missouri State Med. Assn.*, 1921, xviii, 220), who calls attention to the fact that we obtain a cure after operation if we remove the fibroid and the patient survives and is well thereafter. In radiotherapy, on the other hand, we aim at only a *clinical* cure, that is to say, the object to be accomplished is attained, if the menorrhagia caused by the fibroid either ceases altogether or only a scanty or infrequent menstrual flow ensues. Furthermore a reduction in the size of the tumor is a part though not an essential one, of the clinical cure after radiotherapy. With these definitions in mind we

must approach the statistics thus far published. Many thousands of cases of fibroids have already been treated with radium or the roentgen rays, and the results obtained show on the whole a marked similarity. In order not to quote too many figures, the author mentions the collective statistics of 2982 cases of fibroids treated with the roentgen rays, in which there were 95.6 per cent cures and 4.4 per cent failures. In 944 fibroids treated with radium there were 94.4 per cent cures and 5.6 per cent failures. These statistics take into consideration the results obtained in various parts of the world, and they include the cases in which the technic had to be first acquired as well as those in which the technic had attained its present state of refinement. If only the latter kind were tabulated, Gauss and Friedrich found that in 425 fibroids roentgen-ray treatment yielded 98.4 per cent cures and had only 1.6 per cent failures, and exactly the same result was obtained in 372 fibroids treated with radium. It is important to remember that this type of treatment must not be given to fibroids which extend above the umbilicus. Large pedunculated subserous or submucous fibroids are likewise unsuited. In these three categories radiotherapy may produce a necrosis of the tumors. Cervical fibroids are refractory to radioactive treatment. Rapidly growing fibroids suggestive of sarcomatous degeneration, suppurating or gangrenous fibroids, or those in which any other form of degeneration has taken place, are to be operated upon, likewise those associated with carcinoma of the uterus. Fibroids pressing heavily upon the bladder or rectum had better be removed surgically. It is important, therefore, to carefully select the cases which are to be radiated, since the man who administers radiotherapy indiscriminately disregards the best interests of his patients as much as the man who adheres exclusively to surgery.

Observations on Ectopic Gestation.—Any series of 307 cases of ectopic pregnancy must be of interest to the gynecologist but when, in addition to its size, such a series occurs in the practice of and is analyzed by such a surgeon as Polak (*Am. Jour. Obst. and Gynec.*, 1921, ii, 280), it must of necessity contain much of practical importance. His experience has shown that clinically all ectopics fall into two general classes: (1) Those which may be classed as in the non-tragic stage, with a pulse distinctly countable of 100 or under with a systolic pressure of 100 or over and a hemoglobin of 60 per cent or more. In this class there were 263 cases. (2) And those in the tragic stage pulseless at the wirst, with a blood pressure below 90, a hemoglobin under 50 and definite signs of internal hemorrhage and collapse. In this class there were 36 cases. The analysis of this series shows that ectopic pregnancy occurs most frequently where there is a congenital anomaly or a previous inflammation of the tube, in the woman who gives a history of premenstrual dysmenorrhea. Like other pregnancies, there is a period of amenorrhea or an attempt at menstrual suppression, but because of the unstable position of the ovum owing to the imperfectly developed tubal decidua and erosion of the ovum into the underlying muscle and venous radicles, bleeding takes place into the decidua and produces such ovular unrest as to cause tubal distention and peristalsis which is evidenced by colicky pains and uterine bleeding. The bleeding into the decidua plus the growing ovum distends the tube and causes the soreness and tenderness

over the region of the distended gestation sac. The relation of the physical signs to the pathology is still more striking and constant, as was shown by the study of this series. The uterus is enlarged, because it contains a deciduum which was prepared in anticipation for the reception of the ovum. This sign could be definitely demonstrated in all of the ectopic pregnancies of eight weeks or over. The cervix is soft, due to the congestion consequent upon pregnancy. This symptom is variable and is of no diagnostic importance. It was noted in a very few of the cases. Bimanual examination shows that the uterus does not have the usual characteristic diagnostic sign of pregnancy, *i. e.*, the elasticity of the median portion of the anterior wall and the compressibility of its isthmus. The absence of these changes in consistency is due to the absence of the growing ovum in the uterus, which though it is enlarged, is not changed in shape or consistency except for the slight softening of the cervix which is not constantly present. The cervix is exquisitely sensitive to motion. This is shown by palpation and is due to the peritoneal irritation from the blood which gravitates from the end of the tube or through the tubal wall because of its porosity and finally to the prolapse of the tubal mass into the cul-de-sac. This reaction of the peritoneum covering the utero-sacral ligaments makes them sensitive, hence anything which moves these sensitive bands will cause exquisite pain. This sign, pain on movement of the cervix, was present in all of the cases in this series. In considering the proper treatment of ectopic pregnancy, it should be remembered that primary rupture of the tube is not usually serious nor fatal. Less than 1 per cent bleed to death, 3 out of 307 cases in this series from the primary rupture, as the usual erosion goes through an arterial twig, and not the main vessel. Bleeding continues until the blood pressure falls, a clot forms and the bleeding ceases. The patient reacts, feels well for a day or two, and then a secondary rupture occurs and the doctor who has treated her for indigestion has missed the psychological moment to do the operation in the non-tragic stage. Polak's experience, and it has not been inconsiderable, teaches him that the best time to operate is after a reaction. This is shown by the slower pulse and gradual increase of blood pressure. Almost all of these patients will come back with rest and morphine. He gives them an initial dose of $\frac{1}{2}$ grain and $\frac{1}{4}$ grain every three hours, reducing the respirations to eight or twelve, and he has yet to see a case which has not reacted and become a safe operable risk under this treatment. No saline is used until after the operation, then never by infusion. Blood transfusion is preferable when the vessel has been tied, never before; but it is indicated during the procedure in severe cases. The operation consists in properly removing the tube without interfering with the collateral circulation of the ovary. This can only be done by individual ligation of the vessels in the mesosalpinx, not by mass ligature. After the tube is removed, the ovary is suspended by suture of the infundibulo-pelvic ligament to the round ligament and the raw surface at the top of the broad ligament peritonealized by whipping the mesosalpinx and round ligament together. It is only possible by waiting for reaction from shock to select the time for operation, then we can give the woman her best chance both as to mortality and morbidity.

OPHTHALMOLOGY

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Ocular Syphilis in the Second Generation.—SIDLER-HUGUENIN (*Klin. Monatsbl. f. Augenhk.*, January, 1921, p. 44) discusses the question of the transmissibility of syphilis from grandparents to their grandchildren—a long-standing subject of controversy; the proof of such transmissibility is extremely difficult if Finger's requirements are to be satisfied, namely, (1) undoubted hereditary syphilis must be present in the first generation; (2) acquired syphilis in the father and mother of the first generation must be absolutely excluded; (3) the specific affections in the second generation must be indubitably of the form of inherited syphilis. The author considered it preferable, from the standpoint of practice, to limit his researches to an exhaustive examination of all the children born of parents clearly affected with hereditary syphilis; it is precisely in the domain of ophthalmology that the most certain results are attainable in the detection of hereditary syphilis (parenchymatous keratitis with 90 per cent of specific origin, typical alterations of the fundus). The author's material consisted of 250 cases encountered in the course of thirty years in the Children's Hospital of Zürich. Of these 250 cases he has been able to trace 50 couples, one of whose members belonged to the above 250 cases; 36 of these couples had children (only 65 all told) and 14 couples (28 per cent) had none. That the number of families belonging to the 250 cases above mentioned was so small is due to the fact that the subjects almost in their entirety belonged to the floating laboring population and that a precocious mortality of about 50 per cent exists in these cases; moreover, the survivors, frequently invalids, do not ordinarily marry and that their fecundity is very low. First, among the 50 couples, 27 (5 without children) mothers were affected with hereditary syphilis; these 22 couples had 44 children. Second, in the same series 23 fathers (9 sterile) were affected with hereditary syphilis; the entire number of children was 17; thus the genital apparatus in the male appears more vulnerable than in the female. The Wassermann was negative in all the children of both the above categories and the examination of the skeletons by the roentgen rays revealed but a single anomaly; the latter belonged to the first group. Among the anomalies *not strictly specific* the reporter found 2 cases of strabismus, 3 of rickets and 1 of tuberculosis; these dystrophies may as well be ascribed to faulty hygiene and defective alimentation. The one doubtful case is uncertain, for while the mother presented undoubted manifestations of hereditary syphilis, the father gave an uncertain Wassermann. Finger's postulate is accordingly not realized in this case. From these researches the high per-

centage of sterile marriages is very striking, particularly when it is the husband who is the subject of hereditary disease. Eight mothers at the time of conception and during the early months of pregnancy presented severe and indubitable signs of hereditary syphilis; their fourteen children showed no specific stigmata whatever. The author draws the conclusion that parents affected with hereditary syphilis will have none or few children, but that the latter will in all probability be healthy; nevertheless, when an individual affected with hereditary syphilis contemplates marriage it would be in order to subject him to energetic specific treatment prior to that event; if it be the prospective husband, there is absolutely no danger of the transmission of syphilis.

The Eye of the Aged.—MONAUNI (*Arch. d'ophthal.*, March, 1921, p. 180) contributes a study of the senile eye; the reporter concludes that such lesions may be reduced to the following types: Fatty and calcareous degeneration, decrease of the elastic elements and increase of hyaline substance. Fatty degeneration affects all the ocular tissues, especially the fibrous and vascular tunics as well as the refracting media; it attains its maximum in the sclera, the ciliary body and vitreous humor. Calcareous degeneration is more general in the posterior segment of the sclera, in the stroma of the ciliary body and in the vitreous, especially its anterior segment. The fats of the senile eye are, for the most part, constituted by cholesterin; to a less degree by the neutral fats. It is only in the vitreous bodies of the choroid that phosphatic compounds, saturated and non-saturated, are met with. The alterations of the elastic fibers consist in rarefaction of the elastic meshes, narrowing of the fibers and hyaline degeneration. Rarefaction and narrowing of the fibers affect all the ocular tissues as well as the optic nerve; these changes predominate in the cornea and sclera. In the cornea the anterior and posterior limiting membranes are affected with hyaline degeneration; the same is the case with the elastic fibers of the periphery, the choroidal vitreous lamina, capsule of the lens and very probably also the zonula and the large fibers of the vitreous body; the latter constantly show numerous crystals of variable chemical composition. In the explanation of the pathogeny of the *arcus senilis*, besides fat, account must be taken of the alterations of the elastic tissue of the periphery of the cornea, and especially also of hyaline degeneration. The vitreous bodies of the choroid must be regarded as hyaline productions of the vitreous lamina combined with the fats of the subepithelial layer of the choroid; there is present, in addition, a fatty degeneration combined, in all probability, with hyaline degenerations; the same is true of the fibers of the zonula and of the large fibers of the vitreous body; to these alterations is to be attributed the greatest importance in the pathogenesis of certain forms of luxation of the lens, senile synchisis and sparkling synchisis. There is the closest dependence between the lesions of the ocular membranes and those of the bloodvessels. The lesions above mentioned explain the disorders of nutrition and the ocular maladies of senility, as also of the disturbances of accommodation. Based upon the above findings, all more or less characteristic of arteriosclerosis, the writer concludes that the alterations of the senile eye are due, above all other causes, to atheroma; the appellation *cholesteric steatosis* of the senile eye, suggested by Vollaro, is quite suitable for the syndrome.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Value and Mechanism of the Colloidal-gold Test.—After a comprehensive review of the colloidal-gold test, as applied to the examination of spinal fluid by Lange, CRUICKSHANK (*British Jour. Exper. Path.*, 1920, i, 71) detailed the findings of the gold sol, Wassermann and globulin in 27 cases of general paralysis, 1 of juvenile general paralysis, 3 of suspected general paralysis, 1 of taboparesis and 58 miscellaneous cases comprising different mental conditions, chronic dementia, epilepsy, dementia precox, delusional and other insanities. In the cases of general paralysis, the findings agreed with those of other observers in that all cases gave the paretic reaction, the Wassermann tests were positive and various degrees of globulin increase were detected in all instances. In the 57 cases representing various mental conditions, all gave negative Wassermann and gold reactions. As the reacting power of a syphilitic serum or spinal fluid had been shown to reside in the globulin fraction of the protein, paretic fluids were subjected to half saturated ammonium sulphate in order to get rid of albumen, dissolved in salt solution and dialyzed until free from salt. The precipitate of globulin was then dissolved in an amount of 0.8 cc of 5 per cent NaCl solution equivalent to the original volume of spinal fluid. It was found that the globulin had the precipitating power of the original spinal fluid, being even more active, and that the globulin gave positive Wassermann reactions. In 2 cases where the spinal fluid had yielded anomalous gold reactions, the separated globulin gave a paretic reaction in both instances. In this connection, it was learned by experimentation that the dialyzed albumen fraction acted as a protective colloid, which had apparently served to obscure the readings in the original fluid. The globulin from negative spinal fluids did not precipitate the colloidal gold, even in high concentrations, suggesting that the reactions of paretic fluids were not due solely to the increased content of globulin, but to an alteration in the physical or chemical character of the globulin and that the different zone reactions were dependent on the relative amounts of globulin and albumen, as suggested by Felton. The alteration in globulin cannot be regarded as specific for syphilis, since it occurs according to the work of others in multiple sclerosis, but it is interesting that the change is so constant in one and common in another, which is now suspected to be due to a spirochete, the author believing that only reaction of the paretic and luetic types should be regarded as a real diagnostic value and that meningitic reactions, while being of some value in conjunction with other findings

should for the present be held *sub judice*. He states that the reaction in syphilitic diseases of the central nervous system depends on a physical change in the globulin associated with increased positive electric charge.

Summary of Experimental Studies on the Histopathologic Changes Produced by Arsphenamine and Neoarsphenamine.—The fatalities following the administration of arsphenamine and neoarsphenamine in the treatment of syphilis have usually been attributed to the toxicity of the drugs and to technical errors in administration referable to the preparation of the solutions and manner of injection. KOLMER and LUCKE (*Arch. Dermat. and Syph.*, 1920, ii, 289) studied the histopathologic changes produced in rats and rabbits by the intravenous injection of single large and multiple small doses of arsphenamine and neoarsphenamine. The animals were injected intravenously with acid solutions of arsphenamine, with single large (0.08 to 0.1 grams per kilo body weight) and multiple small (0.01 mg. per kilo) doses of solution of disodium arsphenamine. The single large dose corresponded to 4.8 and 6 grams for a person of about 130 pounds and the small dose to 0.6 gram per 130 pounds. From six to seventeen doses were administered. Neoarsphenamine was introduced into rats and rabbits in a single large (0.2 gram per kilo) and in multiple small doses (0.02 to 0.03 gram per kilo). The former corresponded to about 12 grams per 130 pounds and the latter to 1.2 to 1.8 grams per 130 pounds, from six to eighteen doses of the latter being administered. The histological study of the organs removed at necropsy showed that the lesions produced by neoarsphenamine were generally of the same character as those produced by arsphenamine but, in comparison with dosage, were less severe. Acid or non-neutralized solutions of arsphenamine produced several vascular injuries in all organs, characterized by congestion, hemorrhagic extravasations and the production of peculiar thrombi, with secondary cellular degeneration and necrosis. Single large doses of arsphenamine and neoarsphenamine also produced similar vascular changes, but in a milder degree; areas of focal necrosis and cellular degenerations in heart muscle, liver and spleen were rather prominent. The kidney lesions were composed of these vascular changes and varying degrees of tubular necrosis. Multiple small doses of arsphenamine and neoarsphenamine produced slight vascular changes of congestion and thrombi of conglutinated erythrocytes in the various organs; focal areas of cellular degenerations and necrosis were frequently well marked, particularly in heart and liver. The authors emphasize that the maximum changes were produced by large doses of acid solutions of arsphenamine and by doses of disodium arsphenamine and neoarsphenamine so large that they have no analogy to the amounts commonly administered to persons in one dose and at one time.

Dissemination of Spirocheta Pallida in Experimental Syphilis.—With a view to confirm certain observations of earlier workers in the course of routine work in latent syphilis, and to throw some light on the behavior of certain strains which had been isolated from different sources, EBERSON (*Arch. Dermat. and Syph.*, 1921, iii, 111) performed experiments to determine roughly the presence of Spirocheta pallida

in the blood stream and regional lymphatic glands prior to manifestations of syphilis in the inoculated testicles of rabbits. It was found that Spirocheta pallida could be isolated from the blood stream of experimentally infected rabbits seven, ten and thirty days after intratesticular inoculation, at times corresponding to twenty-six, twenty-three and three days prior to the appearance of any initial lesions. Active, virulent Spirocheta pallida were found in the regional lymph glands of rabbits seven days after inoculation of the rabbit's testicle and twenty-six days before any primary lesion had appeared. The spleen was shown to contain Spirocheta pallida more than two months after the inoculated testicle had healed entirely and had been found free from spirochetes by repeated puncture and direct inoculation of the excised testicles in other rabbits. The author believes that for confirmation of experimental work and for diagnosis of suspicious syphilitic material which cannot be studied microscopically, the method suggested by these studies might be employed to advantage. He goes on to say that with early invasion of the lymph glands and blood stream established definitely during the incubation period of syphilis in animals, the theory of a life cycle of Spirocheta pallida is weakened; that the absence of organisms, as judged solely by microscopic findings, is not convincing proof that a change of form has taken place within the animal body and the fact that Spirocheta pallida have been found unaltered both in morphology and in virulence in the blood and glands would seem sufficient to render the theory untenable.

Variations in the Bacterial Flora of the Upper Air Passages in Course of the Common Cold.—Bloomfield (*Johns Hopkins Bull.*, 1921, xxxii, 362–121) presents a bacteriological study of common colds. A previous report of the normal anaërobic flora of the throat in healthy individuals was used as a control series. Cultures from the nasopharynx and tonsils of 10 cases were made during the active stage of coryza and during convalescence. It was found that in uncomplicated cases the flora differed in no fundamental way from that in healthy individuals. Just as in the normal controls, non-hemolytic streptococci and Gram-negative cocci were found to be constantly present, and there occurred a shifting transient flora of diphtheroids, coarse Gram-positive cocci, minute Gram-positive organisms, Staphylococcus albus, etc. However, this transient flora was richer and more varied than in the controls. The author suggests that the explanation of this is that the disturbances of the mucous membrane during the cold allows a general increased activity of bacterial growth, but none of these organisms can be the primary cause of the cold, because they are too variable and inconstant. He concludes that the etiological organism is unknown and is certainly not the streptococcus, which, however, acts as secondary invaders in local complications.

Experimental Production of Clinical Types of Syphilis in the Rabbit.—Of late the tendency has been to lay more and more stress on the disease-producing properties of the organism concerned rather than the reactive mechanism of the host. The factors that determine these features of the disease may be numerous, and the results of their action differ so widely that diversity rather than uniformity has come to be

recognized as one of the most fundamental characteristics of syphilis. Inasmuch as the causes which underlie this diversity of clinical types are but little understood, BROWN and PEARCE (*Arch. Dermat. and Syph.*, 1921, iii, 254), utilizing a modified conception of the theory of inhibition, altered the defensive mechanism in different ways in order to produce types of disease that would conform to alterations in the mechanism of animal resistance, the infecting organism being maintained as a constant factor in the reaction. Forty-four rabbits were inoculated in the testes with the Nichols strain of Spirocheta pallida, using for each testicle 0.5 c.c. of an emulsion containing many spirochetes. In half the rabbits, both testes were inoculated. Each series was then divided into four groups. One group of 6 animals served as controls where the infection was permitted to progress without any interference. In a second group of 5 rabbits the testes were removed fourteen days after inoculation while in a third group, also of 5 rabbits, castration was performed twenty-eight days after inoculation. In the fourth group of 6 animals temporary therapeutic suppression of the testicular reaction was accomplished by a single intravenous injection of arsenophenylglycyl dichlor-m-aminophenol. All animals were observed for from three to three and a half months after inoculation. It was found that by early and radical interference (castration) it was possible to so alter the course of the disease as to cause bone lesions practically to supplant those of the testes in the defensive reaction, while, conversely, by permitting the testicular reaction to progress to a given point, it was possible to confer protection on this group of structures. In this case no bone lesions occurred but the generalized disease began with involvement of the next group of tissues in order, producing an infection essentially of skin, mucous membranes and eyes. It was also found that while in most animals inoculated in both testes a high degree of protection was seemingly conferred on other tissues in many instances, the protection failed to reach the eyes, lesions of the cornea and iris appearing as only clinical manifestations of a generalized disease—an observation which, as the authors suggest, might explain such conditions as neurosyphilis, in that certain tissues may fail to receive protection.

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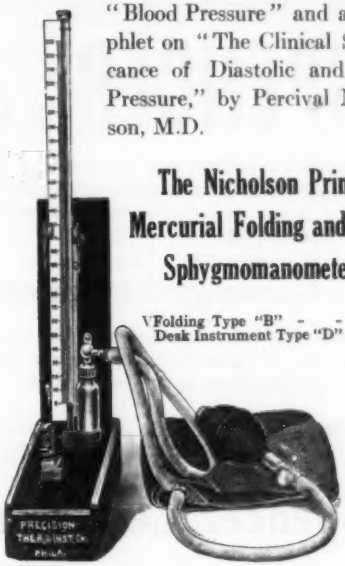

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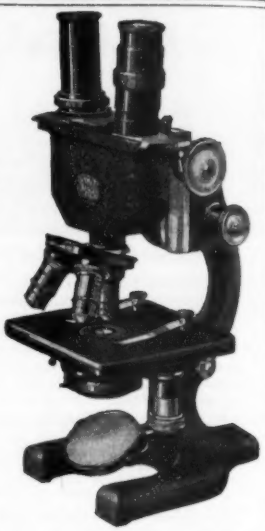

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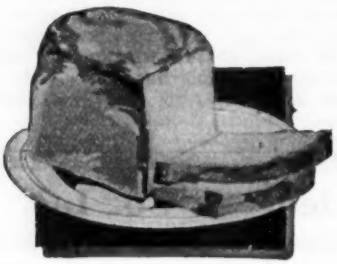

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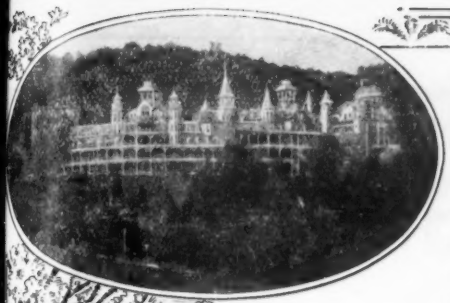

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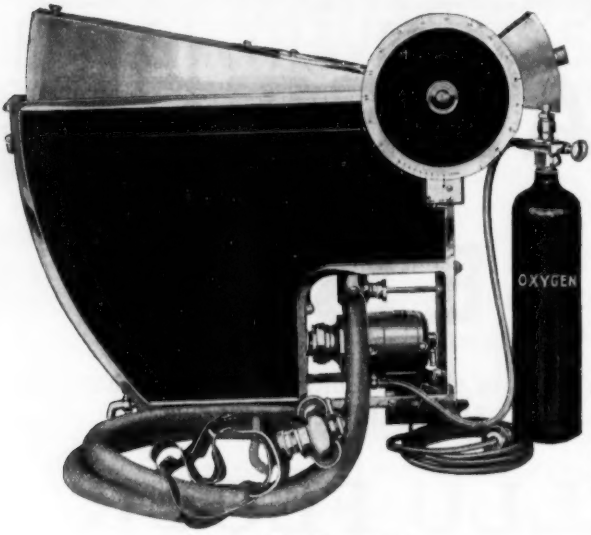

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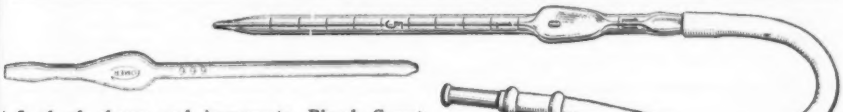

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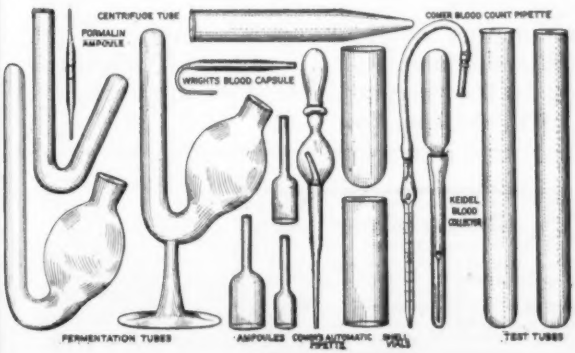

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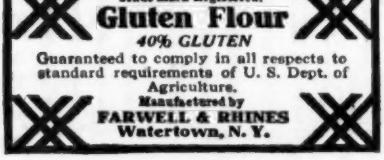
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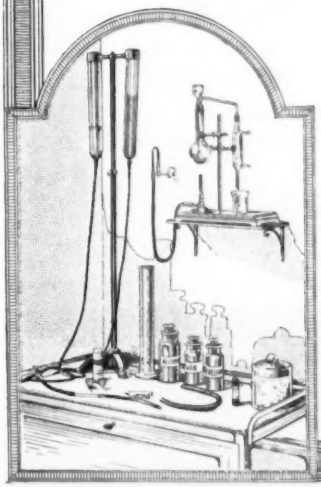

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